A Probabilistic Assessment of the Risk of Brodifacoum to Non-target Predators and Scavengers

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by

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Summary

This document presents the results of an analytical approach for estimating the risk to predators and scavengers from use of brodifacoum-containing baits for control of commensal rodents. The risk assessment was designed to provide quantitative answers to the questions: ***Under various brodifacoum use scenarios, what is the likelihood that a non-target predator or scavenger will ingest a lethal dose through consumption of animals that have been exposed to brodifacoum? What is the uncertainty in the brodifacoum-related mortality rate for these predators and scavengers?***

This assessment was based upon (1) a dietary dose model to estimate the ingestion of brodifacoum by non-target animals and (2) an effects model to estimate the relationship between brodifacoum exposure and effects on the animal. Five species were selected as surrogate non-target species for the risk assessment: coyote (*Canis latrans*), red fox (*Vulpes vulpes*), kit fox (*Vulpes macrotis*), red-tailed hawk (*Buteo jamaicensis*), and great horned owl (*Bubo virginianus*). For each non-target species, the dietary exposure model was used to estimate daily dose as a function of body weight and food ingestion rate, taking into account the concentration of brodifacoum residue in food and the fraction of brodifacoum-containing food in the diet. The exposure model incorporated field data on residue concentrations in rodents and the fraction of rodents in the diets of predators. In the effects analysis, a standard logistic dose-response relationship was generated for each tested species based on laboratory data. The multispecies data also were integrated to estimate dose-response relationships for hypothetical high sensitivity species (upper 10 percent of sensitivity), median sensitivity species, and low sensitivity species (lower 10 percent of sensitivity). Risk was estimated by combining exposure and effects distributions to estimate the probability of mortality for non-target species.

A sensitivity analysis indicated that risk of mortality was strongly influenced by the proportion of rodents in the diet that have been exposed to brodifacoum, and by uncertainty about the sensitivity of the surrogate species to brodifacoum. The table below compares the estimated mortality rates for the surrogate species at the 10%, 50%, and 90% exceedence levels, assuming median sensitivity and 1% exposed rodents in the diet (considered an overestimate in most situations).

Summary Table: Estimated risk of brodifacoum to five surrogate non-target species, assuming median sensitivity for all species and 1% exposed rodents in their diets.

Species	Estimated Mortality Rate (%)		
	10% exceedence probability	50% exceedence probability	90% exceedence probability
Coyote	2[a]	≤1	≤1
Red Fox	≤1	≤1	≤1
Kit Fox	5	≤1	≤1
Red-Tailed Hawk	2	≤1	≤1
Great Horned Owl	7	2	≤1

[a] Interpretation: there is a 10% probability that the coyote mortality rate exceeds 2% under the assumptions of this model run.

The risk of brodifacoum-induced mortality is low in coyote, red fox, and red-tailed hawk, and by inference the same conclusion applies to other species of birds and mammals with similar dietary composition and metabolism. Risk is slightly greater for species with a higher percentage of rodents in their diet, such as the kit fox and great horned owl.

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1 Introduction

Brodifacoum (3-[3-(4'-bromo-[1,1'-biphenyl]-4-yl)-1,2,3,4-tetrahydro-1-naphthalenyl]-4-hydroxy-2H-1-benzopyran-2-one) is an effective second-generation anticoagulant rodenticide primarily used to control Norway and roof rats and house mice, including warfarin-resistant rats and mice. Brodifacoum is the most widely used rodenticide in the US accounting for approximately 93% of all over the counter rodenticide sales (Kaukeinen et al. 2000).

Information from laboratory and field studies suggests that some birds and non-target mammals might suffer fatal effects by ingesting carcasses or living prey containing brodifacoum residues (see reviews by Colvin et al. 1988; U.S. EPA 1998b; Erickson and Urban 2002)[1]. However, laboratory experiments indicate only the potential for effects, not their likelihood of occurrence in the field. Field observations suggest that rodenticide poisoning incidents may occur, but the data are insufficient for estimating the probability of adverse effects on non-target species (Luttik et al. 1999). Risk depends on many factors, especially the feeding preferences of predators and scavengers, and availability of live rodents and carcasses. "Such data is difficult to describe quantitatively. Moreover, it depends strongly on local conditions, making risk assessments a demanding task" (Joermann 1998).

The U.S. Environmental Protection Agency (U.S. EPA 1998b) reviewed data concerning brodifacoum and five other rodenticide active ingredients and concluded that brodifacoum uses "with additional labeling requirements and a number of risk mitigation measures, will not cause unreasonable risk to humans or the environment." EPA noted, however, that the Agency had received incident data suggesting possible risk to non-target species. After issuing the Reregistration Eligibility Decision (RED) authorizing reregistration of brodifacoum-containing products (U.S. EPA 1998b), EPA conducted a comparative assessment of nine rodenticides currently used in the United States (Erickson and Urban 2002). In the comparative assessment, EPA concluded that brodifacoum poses a greater primary and secondary hazard to birds and mammals than the other active ingredients examined. However, the comparative assessment included only a limited consideration of exposure, and therefore did not estimate quantitative risk.

To more accurately estimate the probability and magnitude of potential ecological impacts of brodifacoum, four rodenticide registrants (Bell Laboratories, Inc., LiphaTech, Reckitt Benckiser, and Syngenta Crop Protection) contracted The Cadmus Group, Inc. to conduct a probabilistic ecological risk assessment. This document is the report of the methods and findings of that assessment.

[1] As discussed in Section 2.2.1, this study does not address the potential risks of accidental poisonings of non-target species that might ingest brodifacoum from bait stations.

2 Problem Formulation

Problem formulation is "a process for generating and evaluating preliminary hypotheses about how and why ecological effects have occurred, or may occur, from human activities" (U.S. EPA 1998a). The problem formulation integrates available information and produces three components: assessment endpoints, a conceptual model, and an analysis plan. The problem formulation thus defines the objectives of the risk assessment, describes the relationships between the chemical and species potentially at risk, and outlines the approach to be used for analyzing data and estimating risk.

The problem formulation was updated several times to incorporate suggestions from other scientists and insights gained during development of the model. In the following discussion we indicate the most significant of these revisions where relevant, and we explain our decisions about the scope of the assessment.

2.1 Assessment Endpoints

Assessment endpoints are "explicit expressions of the actual environmental value that is to be protected, operationally defined by an ecological entity and its attributes" (U.S. EPA 1998a). Criteria used to select assessment endpoints include ecological relevance, susceptibility to the stressors of concern, and relevance to management goals. The endpoints for this assessment were selected based on the potential pathways of exposure and professional judgment regarding the ecosystem components under consideration.

Granivorous, omnivorous, and carnivorous birds and mammals are believed to be the animals most likely to consume brodifacoum baits or brodifacoum-poisoned rodents, and birds and mammals are known to be sensitive to the toxic effects of brodifacoum. While certain invertebrates (e.g., beetles, roaches, and ants) are likely to be exposed to brodifacoum, they do not appear to be sensitive (Morgan et al. 1996). Granivorous, omnivorous, and carnivorous birds and mammals are ecologically important in virtually all terrestrial habitats. The attributes of these animals that are relevant to ecological management goals are individual survival and population abundance. ***The assessment endpoints are thus: (1) individual survival of birds and mammals, and (2) population abundance of birds and mammals.***

Due to the mode of action and acute toxicity of brodifacoum, non-target mortality is considered the most relevant factor potentially affecting these assessment endpoints. Lethal poisoning, as well as direct sublethal effects that could increase the likelihood of individual mortality (e.g., hemorrhaging), are of greatest concern. This risk assessment is designed to provide a quantitative answer to the questions***: Under various brodifacoum use scenarios, what is the likelihood that a non-target predator or scavenger will ingest a lethal dose through consumption of animals that have been exposed to brodifacoum? What is the uncertainty in the brodifacoum-related mortality rate for these predators and scavengers?*** The answers to these questions can be used to infer the likelihood of widespread and repeated mortality of non-target birds and mammals.

As mentioned, assessment endpoints are intended to link the assessment to risk management goals. The goals themselves incorporate social, economic, and cultural values as well as scientific knowledge. They are established by legislators and regulatory policy makers, and vary in their application depending on site, habitat, and other factors. Determinations of acceptability — consistency with protection goals — are also made by regulators and risk managers, not risk assessors. The purpose of the risk assessment is to provide decision makers with relevant information about the magnitude and likelihood of ecological effects, thereby enabling informed decisions about acceptability of risk.

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2.2 Conceptual Models

A conceptual model in a risk assessment problem formulation is "a written description and visual representation of predicted relationships between ecological entities and the stressors to which they may be exposed" (U.S. EPA 1998a). The conceptual models in this risk assessment have two principal purposes: (1) to express the assumptions about the factors affecting exposure and risk to non-target birds and mammals, and (2) to provide a framework for developing the mathematical analysis.

The conceptual models for this risk assessment consist of three components. A general model of brodifacoum movement through the food web (Section 2.2.1) depicts the major pathways by which non-target animals may be exposed to brodifacoum residues. A dietary dose model (Section 2.2.2) estimates the ingestion of brodifacoum by non-target animals as a function of body weight, food ingestion rate, brodifacoum concentration in food, and the fraction of brodifacoum-containing food in the diet. An effects model (Section 2.2.3) expresses the relationship between brodifacoum exposure and effects on the animal.

2.2.1 Brodifacoum movement through the food web

Potential routes of exposure of non-target animals to brodifacoum residues are shown in Figure 1. Brodifacoum bait may be consumed by target rodents and by non-target animals that feed on pelleted or wax block baits (primary exposure). Predators and scavengers may be exposed to brodifacoum by feeding on target and non-target animals or carcasses containing brodifacoum residues (secondary exposure).

We concluded that other pathways of non-target exposure were probably much less significant than dietary exposure. For example, excretion of brodifacoum by bait feeders could result in contamination of soil, creating the possibility of subsequent dermal or oral exposure (Larsen 2003), but the high organic carbon partition coefficient of brodifacoum (10,000 to 52,000, depending on soil type) implies that brodifacoum residues in soil are not readily bioavailable. The low solubility of brodifacoum in water (0.24 mg/L) implies that exposure of non-target animals via drinking water would be insignificant. Brodifacoum's very low vapor pressure ($<<10^{-8}$ mm Hg at 20^{o}C) implies that inhalation exposure also would be insignificant.

Primary exposure to non-target animals that ingest rodenticide baits was not included in the scope of the risk assessment. The decision to limit the assessment to secondary exposure was based on several practical and conceptual considerations:

- Risk of secondary exposure to predators and scavengers appears to be of greater concern to regulators than risk of primary exposure to non-target bait feeders.
- A fundamentally different exposure model would be required to assess primary exposure, because a different approach would be needed to estimate the proportion of brodifacoum-containing food in the diet.
- Risk reduction for non-target bait feeders is essentially a matter of bait station design and placement.

Some predators may be exposed to brodifacoum through consumption of invertebrate bait feeders such as beetles and ants. However, we considered exposed rodents to be a more significant source of brodifacoum to predators and scavengers under most circumstances. The risk assessment therefore focused solely on secondary exposure through consumption of rodents, and did not explicitly address exposure through invertebrate food items.

2.2.2 Brodifacoum dose to non-target species

Figure 2 depicts a conceptual model of brodifacoum exposure to a non-target species using owls in a rural habitat as an example. The figure shows a section of rural landscape including woodlands, cropped fields, pasture, wetland, and farm buildings. Brodifacoum bait is in use on a percentage of farms at any point in time. The owls' prey includes rats (some of which are exposed to brodifacoum) and alternative prey. Preferences for foraging habitat and prey, and the spatial distributions of habitats and prey populations, determine the diet of each owl. All of these factors are likely to vary over time.

We considered a number of strategies for estimating the fraction of brodifacoum-containing food in the diet of a predator or scavenger. Some approaches were based on feeding behavior and habitat preferences, which are difficult to quantify and simulate, or on demographics and landscape, which can be quantified (with effort) but are highly site-specific. We decided to use direct measurements — readily available field data on the dietary composition of each species — instead of complex behavioral simulations.

A dietary dose model, similar to those presented by Pastorok et al. (1996), Sample et al. (1997), and ECOFRAM (1999b), was used to estimate daily dose as a function of the body weight and food ingestion rate of the animal, the concentration of residue in food, and the fraction of brodifacoum-containing food in the diet. A simple uptake-depuration model was then used to estimate the cumulative dose over time. These models are described in Sections 3.2 and 3.3.

2.2.3 Brodifacoum effects

A number of publications review the mode of action of rodenticides, including brodifacoum (Ford 1993; WHO 1995; Howald 1997; Howald et al. 1999; Erickson and Urban 2002). Brodifacoum inhibits the normal synthesis of vitamin K-dependent clotting factors in the liver, leading to in an increase in blood clotting time, hemorrhaging, and death. The relative potency of anticoagulant rodenticides is dependent on their affinity to bind a common site in the liver (Parmar et al. 1987; Huckle et al. 1988). Brodifacoum, a second-generation anticoagulant, generally provides a lethal dose after a single feeding, although death is usually delayed 5 to 10 days (Erickson and Urban 2002). During this time animals may continue to feed if bait is available. The time to death is dependent not only on the coagulation time but also on the frequency and size of hemorrhage likely during normal activities.

Elimination studies indicate that brodifacoum exists in the animal in two internal pools: a rapidly eliminated pool and a pool (mainly in the liver) which is eliminated very slowly. When the liver binding sites are saturated (at about 0.7 mg brodifacoum/kg liver), additional exposure can result in a toxic effect (Kaukeinen et al. 2000). However, because data available on the toxicokinetics of brodifacoum are limited even for the target rodents, we applied a simplified conceptual model based on whole body concentrations, assuming a single internal pool and first-order depuration kinetics. A standard logistic model (see Section 4.2) was used to quantify the dose-response relationship between whole body concentration and mortality.

2.3 Analysis Plan

The following analysis plan summarizes the approach for estimating brodifacoum risk. The analysis plan has five components:

1. Select scenarios for brodifacoum usage;
2. Select surrogate non-target species;
3. Estimate dietary dose of brodifacoum to each surrogate species (exposure analysis);
4. Estimate effects of brodifacoum exposure on each surrogate species (effects analysis);
5. Estimate risk by combining exposure and effects estimates and extrapolating to the assessment endpoints.

These components are discussed individually in the following sections.

2.3.1 Usage scenarios

Rodenticide baits containing brodifacoum are registered only for control of commensal rodents. Label instructions specify that baits are to be used in and around buildings and transport vehicles, and inside sewers (Erickson and Urban 2002). Actual baiting practices are not well documented. Initially, we expected the model to use information about the amount of bait used, spatial extent of baiting, duration of baiting, and dates of bait use in urban,

suburban, and rural environments. However, such information was not readily available. Surveys could be made of rodent control experts, retail distributors, and homeowners to obtain information about rodenticide usage and baiting practices in cities, suburbs, and rural areas. However, this was not undertaken for purposes of this risk assessment, which relied upon previously generated data.

Outdoor urban uses consist of rodent control around waste containers, restaurants, apartment buildings, warehouses, garages, transportation terminals, and other structures. Urban use is presumably widespread, frequent, and sustained. Urban use could be characterized by use density, i.e., the number of placements or total amount of bait per unit area of urban habitat.

In rural settings, baits are used around barns, silos, and other farm buildings. Application in the open field away from buildings is misuse (i.e., contrary to the product label) and was not considered in this risk assessment. "Rural applications expose a greater diversity of nontarget wildlife to potential hazards of both primary poisoning…and secondary poisoning" compared to use in cities (Mendenhall and Pank 1980). Rural use could be characterized in terms of the fraction of farms where bait is used, and the total amount of bait per farm, measures that are expected to vary seasonally.

Suburban environments are the interface between urban and rural habitats. It is a "common pattern of residential development…for houses to be erected on large lots in prime wildlife habitat on the outskirts of cities and suburbs" (Stone et al. 1999). Though suburban bait uses are probably similar to (but less dense than) urban uses, suburban uses could result in exposure of rural wildlife. Suburban use could be characterized in the same way as urban use (areal density), and is expected to vary seasonally (more use in winter).

Indoor uses of brodifacoum baits were not considered explicitly, because the risk they pose to non-target animals (other than humans and pets) is likely to be much lower than the risk of outdoor uses. Indoor uses present substantially less opportunity for secondary exposure than outdoor uses, because fewer exposed rodents would be present outdoors. Because our secondary exposure model was based on data collected during outdoor baiting programs, the results were presumed to overestimate risk from indoor uses.

The risk of secondary poisoning of wildlife is a function of the frequency of encounters with brodifacoum-containing food (prey or carrion). Early drafts of the analysis plan considered three generic usage scenarios representing urban, rural, and suburban (urban-rural border) habitats. We hypothesized that rodenticide use, target species populations, and non-target diets would vary among habitats. Factors to be considered in estimating exposure might include location of bait placement (next to outside wall, away from walls, in burrows, etc.), density of bait placement, timing and frequency of bait placement, and accessibility of bait to non-target vertebrates. However, because very little information on these factors was available, the model as it was finally implemented was not habitat-specific. In the absence of data, distinctions between exposure in urban, suburban, and rural habitats would have to be based on assumptions. While these factors were not represented explicitly in the exposure model, assumptions about their overall impact on frequency of encounters with brodifacoum-containing food were represented by the variable PT (see Section 3.2.2.5).

2.3.2 Surrogate species

The risk assessment focused on selected surrogate species of birds and mammals. The main criterion for selection of surrogate species was a high presumed level of exposure, based on diet and habitat. Other criteria considered in selection of surrogate species included ecological significance, cultural value, and incident reports.

In our initial analysis plan, we considered selecting surrogate species for each of six categories: avian and mammalian species each representing bait feeders, predators, and scavengers. For reasons outlined above (Section 2.2.1), non-target bait feeders were later excluded from the scope of the risk assessment. Moreover, the distinction between predators and scavengers also was abandoned. Many birds and mammals that prey on rodents also consume carrion occasionally. Field reports on dietary composition rarely distinguish live prey from carrion. Our exposure analysis was based on residue data from carcasses, which we considered to overestimate the residue concentrations in live rodents captured by predators.

To develop the model, we selected candidate species (conforming to the criteria summarized above) for which data were readily available. A great deal of information about the diets of birds and mammals can be found in the open literature. The U.S. EPA and the California EPA have compiled wildlife exposure factor tables containing dietary information as well as other useful data for several dozen species (U.S. EPA 1993; California EPA 2003). We reviewed the data in these tables and selected the five species for whom rodents comprised a significant component of the diet. These species were coyote (*Canis latrans*), red fox (*Vulpes vulpes*), kit fox (*Vulpes macrotis*), red-tailed hawk (*Buteo jamaicensis*), and great horned owl (*Bubo virginianus*). Data on additional species can be extracted from the open literature; for example, we have obtained primary sources and begun compiling data to develop risk estimates for other owls.

For each species selected, we found quantitative information in the exposure factor tables on body weight, ingestion rate, and dietary composition. Information on sensitivity to brodifacoum, such as dose-response relationships, would have been extremely helpful. However, no toxicity data were found for any of the species under consideration as surrogate species. The risk assessment was therefore carried out under alternative assumptions about the sensitivity of the surrogate species, inferred from the distribution of sensitivities of the tested species (Section 2.3.4).

All of the animals selected are typical of rural habitats, and might also live or forage in suburban or occasionally urban habitats (especially if food is scarce in their preferred habitats). Profiles of the selected species follow.

2.3.2.1 Coyote (*Canis latrans*)

The coyote is found through most of the US, western Canada and Alaska. Coyotes inhabit prairies, open woodlands, and brushy areas. Their feeding habits are similar to red fox (see below) but coyotes may also hunt larger prey in pairs (U.S. EPA 1993).

2.3.2.2 Red fox (*Vulpes vulpes*)

The red fox is the most widely distributed carnivore in the world, found throughout most of North America except for the southeastern US. The occupy a wide range of habitats, including farmland, pasture, and hardwood and coniferous forest. Red foxes are nocturnal, preying extensively on meadow voles, mice, and rabbits, as well as other small mammals, insects, birds, and occasionally plant matter. They are also scavengers on carcasses or refuse. Red foxes are territorial, with territories ranging from less than 50 to over 3,000 hectares (U.S. EPA 1993).

2.3.2.3 Kit fox (*Vulpes macrotis*)

The kit fox is found in open prairies, arid grasslands, scrublands, and deserts in the southwestern U.S. Primarily nocturnal, the kit fox feeds on small mammals such as kangaroo rats, mice, squirrels, birds, and occasional reptiles, insects, and plant matter. Kit foxes are territorial, with underground family dens (Canid Specialist Group 2000; Brown et al. 2004).

2.3.2.4 Red-tailed hawk (*Buteo jamaicensis*)

Buteo hawks, of which the red-tailed hawk is the most common species, are the most common daytime avian predators on ground-dwelling vertebrates. Red-tailed hawks inhabit woodlands, wetlands, pastures, prairies, and deserts. Red-tails are opportunistic feeders, with small mammals (mice, shrews, voles, rabbits, and squirrels) the most important prey. They are territorial throughout the year, with home ranges from a few hundred hectares to over 1,500 hectares depending on the habitat (U.S. EPA 1993).

2.3.2.5 Great horned owl (*Bubo virginianus*)

Great horned owls are one of the most widespread and common owls in North America. They occupy a wide variety of habitats including forests, deserts, farmland, woodlands, and city parks. They are nocturnal and feed on rabbits, rodents, and other small mammals as well as birds, insects, and crustaceans (Houston et al. 1998; USGS 2004).

2.3.3 Exposure analysis

The basic exposure model (Section 3.2) was similar to those presented by Pastorok et al. (1996), Sample et al. (1997), and ECOFRAM (1999b). The equation can be applied to a wide range of dietary exposure situations. The model estimated dietary dose as a function of the body weight and food ingestion rate of the animal, the concentration of brodifacoum residue in food, and the fraction of brodifacoum-containing food in the diet.

For many animals, food ingestion rate (FIR) can be estimated reliably using allometric equations based on body weight, such as those described in the Wildlife Exposure Factors Handbook (U.S. EPA 1993) and the Cal/Ecotox Exposure Tables (California EPA 2003). Body weights for each focal species were extracted from the scientific literature. Natural variability in body weight and food ingestion rate was estimated, and the parameters were represented as distributions in the exposure model.

Concentrations of brodifacoum residues in food (i.e., poisoned rodents) were determined from reported results of field studies. Variability in brodifacoum residue concentrations was estimated, and concentrations were represented as distributions in the exposure model. The availability of field data on residues in rodents greatly simplified the exposure analysis. Earlier drafts of the analysis plan had assumed that submodels would need to be developed to estimate concentrations in food.

The fraction of brodifacoum-containing food in the diet was represented in the exposure model (as in those mentioned above) by two variables, PD, the proportion of rodents in the diet, and PT, the proportion of rodents in the diet that have been exposed to brodifacoum. Both variables are largely determined by the behavior of the focal species and the characteristics of the habitat. Initially we considered deriving estimates for PD and PT by simulating foraging behavior. However, a mechanistic model of predator and scavenger behavior could become extremely complex and involve many assumptions. We chose to use field data on dietary composition to estimate PD, rather than to reconstruct dietary composition through simulation of feeding behavior. PT in the standard pesticide model refers to the fraction of an animal's diet that is taken from the treated area – assumed equal to the fraction of time spent in the treated area. In the rodenticide exposure model, PT referred to the fraction of rodents in the diet that have been exposed to baits.

The dietary exposure model estimated the dose of brodifacoum to an animal during one daily feeding interval. To calculate the cumulative dose to an individual over the course of many feeding intervals, a simple uptake-depuration model was implemented. Uptake on a given day was estimated as described above. Depuration (loss from the body by excretion and metabolic transformation) was calculated for the time between feedings, then the next day's uptake was added. These calculations were repeated for a selected period of time (usually 90 days), and the maximum concentration that occurred in the animal's body during the simulation period was recorded as the endpoint of the analysis.

Depuration kinetics of brodifacoum are complex, as described in Sections 2.2.3 and 3.3.2.2. Studies in rats suggest that depuration follows a biphasic curve (Kaukeinen et al. 2000). The

initial phase of the curve is steep, with a halflife on the order of a few days, reflecting a pool of rapidly eliminated brodifacoum in the body. The second phase of the depuration curve is much slower, with a halflife on the order of many months, reflecting a much smaller pool of tightly bound brodifacoum in the liver. However, the toxicokinetics of brodifacoum, particularly the rates of exchange between blood, liver, and other tissues, have not been quantified even in the rat. Many mechanistic and quantitative assumptions would be needed to simulate the biphasic depuration process, and the results would reflect large uncertainties in these assumptions. We therefore chose to simplify the representation of depuration by assuming a first-order model, recognizing that this decision introduced some uncertainty into the analysis. We explored the consequences of this uncertainty by conducting sensitivity analyses using a range of halflife values.

2.3.4 Effects analysis

Effects of brodifacoum on non-target birds and mammals were estimated based on results of standard laboratory toxicity tests. A thorough search of the available literature was conducted to obtain information on the effects of brodifacoum on rats, mice, and non-target species. Searches were conducted using the Syngenta Scientific Archive Management (SAM) database. Library searches for publications on brodifacoum were also conducted. Other sources examined included the 2002 EPA Pesticide Toxicity Database (U.S. EPA 2002), EPA's *Potential Risks of Nine Rodenticides to Birds and Nontarget Mammals: A Comparative Approach* (Erickson and Urban 2002), and EPA's *Reregistration Eligibility Decision (RED) Rodenticide Cluster* (U.S. EPA 1998b). Raw dose-response information and associated reported toxicity test endpoints (e.g., LD50 and confidence interval) retrieved from the search are presented in Appendix B. For some tests, dose-response information was not available and only the toxicity endpoint was included in the database.

The effects data were reviewed for data quality. Prior to evaluating the data, a list of data quality criteria were developed for test acceptability. Tests that did not meet the test acceptability criteria were excluded from the analysis. The test acceptability criteria follow:

- Tests must have a complete dilution series that spans concentrations with little or no effect to concentrations near 100% effect.
- The number of organisms tested at each dilution must be sufficient to define the dose-response relationship.
- The data should exhibit a monotonic (or nearly monotonic) dose-response curve.
- A dose-response model must be derived from the test-specific data. Tests resulting in data that did not allow model fits were not used.
- Tests must result in the calculation of an LD50. Under current EPA test guidelines, the LD50 is argued to be a more appropriate risk assessment endpoint than the LC50 (Mineau et al. 1994; Mineau et al. 2001). Toxicity tests resulting in LC50s (a few studies, mainly with rats) were not used in this risk assessment. Likewise, exposure was calculated in terms of dose to the animal, not concentration in the diet. LC50 values can be converted to LD50s if assumptions are made about food ingestion

during the test, but we considered that the uncertainty introduced by those assumptions would outweigh the loss of information caused by excluding LC50 data.

The single-species dose-response data were analyzed using a logistic model (see Section 4.2). Uncertainty about the model coefficients can be translated into uncertainty about the estimated response at a given dose, or about the dose required to produce a given response.

The dose-response relationships for brodifacoum were assessed for individual test species as described above. However, toxicity data were not available for any of the surrogate species used in the risk assessment. Instead, it was necessary to estimate the sensitivity of untested species based on the distribution of sensitivity of tested species. Species sensitivity distributions (SSDs; Posthuma et al. 2001) represent an effects distribution across species that respond to a chemical in a similar way. Using the standard methods of deriving SSDs, the area under the effects curve represents the variability in response to brodifacoum for a fixed toxicological endpoint (e.g., LD50). However, rather than estimating the distribution of LD50s in this way, we derived the entire dose-response curves corresponding to hypothetical low sensitivity, median sensitivity, and high sensitivity species. Low sensitivity species and high sensitivity species were defined as those with LD50s at the 90^{th} percentile and 10^{th} percentile, respectively, of the SSD. This approach applied a Bayesian hierarchical modeling framework (Section 4.2) developed by The Cadmus Group (Warren-Hicks et al. 2003). In the absence of toxicity data for the surrogate species, the dose-response curve of each surrogate species was represented by the integrated dose-response curve of the low, median, or high sensitivity species (derived separately for birds and mammals).

2.3.5 Risk characterization and extrapolation to assessment endpoints

The risk of brodifacoum to non-target predators and scavengers was estimated by combining exposure and effects distributions to estimate the probability of mortality for non-target individuals. Exposure and effects distributions for each surrogate species and exposure scenario were integrated to generate a distribution of risk usually called a risk curve or Joint Probability Curve (ECOFRAM 1999a). This was done by determining (from the dose-response model) the dose expected to cause a given mortality rate, then querying the exposure distribution to determine the likelihood of that dose being exceeded. This process was repeated for each of a closely spaced series of mortality rates ranging from near zero to near 100%, to derive enough points to describe the complete risk curve (see Section 5.1).

The exposure distributions used in the risk characterization were the full set of cumulative dose estimates (10,000 estimates, 100 for each of 100 individuals) from each run of the cumulative dose model. These distributions combined the variability of potential outcomes for each individual and the variability among individuals, under the assumptions of the daily dose and cumulative dose models (such as proportion of exposed rodents in the diet, depuration halflife, and sensitivity of the surrogate species to brodifacoum).

The effects distributions used in the risk characterization were the estimated dose-response curves for a hypothetical low sensitivity, median sensitivity, and high sensitivity species.

These curves corresponded to the estimated 10th percentile, median (50th percentile), and 90th percentile species on the SSD, as described above (Section 2.3.4).

Risk was expressed in terms of the probability that an individual receives a lethal dose of brodifacoum over a specified period of time. This quantity also can be interpreted as the brodifacoum-related mortality rate among groups of individuals of the surrogate species. The risk curves generated from these distributions indicated the probability of exceeding a specified brodifacoum-related mortality rate, under the combined assumptions of the exposure model and the effects analysis. For example, a particular risk curve might present information on the exceedence probability of mortality rates for coyote, assuming (a) 1% of the rodents in an individual's diet have been exposed to brodifacoum; (b) brodifacoum concentrations in the coyote body decline with a 50-d halflife; and (c) the dose-response curve for coyote is the same as the integrated curve for a high-sensitivity hypothetical species.

The assessment endpoints established at the beginning of the Problem Formulation (Section 2.1) were individual survival and population abundance of omnivorous and carnivorous birds and mammals. The quantitative output of the risk model was expressed directly in terms of individual survival, or brodifacoum-related mortality rate. Effects on population abundance were not estimated, but must be inferred from the mortality rate. Population dynamics, especially of predators, often are determined by density-dependent factors such as competition for nesting sites or foraging territories. Density dependence tends to dampen the population-level impacts of individual mortality, because death of one individual simply confers a greater opportunity for survival to another individual. Thus, effects on population density would be smaller than effects on individual survival and mortality rate. If this generalization applies to the surrogate species used in this assessment, the estimated risk to individuals (the model output) can be interpreted as an upper limit for risk to population abundance of the same species. Exceptions would be expected for populations with densities far below the carrying capacity of the environment.

3 Exposure Analysis

3.1 Overview of the Exposure Model

The exposure model was designed to estimate the concentration of brodifacoum in the body of a predator or scavenger whose food may contain brodifacoum residues. The model was implemented in two stages. Stage 1 calculated a ***daily dose*** of brodifacoum to an individual predator or scavenger. Stage 2 calculated the ***cumulative dose***, the concentration of brodifacoum accumulated in the body of the individual over many days. The analysis addressed the following questions:

Stage 1: daily dose
(1) How much food does a coyote eat each day?
(2) What fraction of that food consists of rodents?
(3) What fraction of those rodents have been exposed to brodifacoum baits?

(4) What is the concentration of brodifacoum in rodents exposed to baits?

Stage 2: cumulative dose
(5) How quickly is brodifacoum eliminated from the body of the coyote?
(6) What is the highest concentration of brodifacoum in the body of the coyote over a 90-day period?

The basic model, described below, could be implemented either deterministically or probabilistically. In its deterministic form, each variable in the model would be represented by a constant and a single exposure estimate would be generated. In the probabilistic form used in the current assessment, most of the model variables were represented by distributions of values, and a distribution of exposure estimates was generated. The model was implemented in a fashion that allowed the calculation of exposure probability for a single individual, as well as variation among individuals.

3.2 Stage 1. Daily Dose Model

3.2.1 Model equations

The basic dietary dose model, similar to those described by Pastorok et al. (1996), Sample et al. (1997), and ECOFRAM (1999b), is shown in Equation 1.

Equation 1

$$DD = FIR \times PD \times PT \times C$$

where

DD = dietary dose (mg brodifacoum/kg body wt/d)
FIR = food ingestion rate (g fresh wt/g body wt/d)
PD = proportion of diet that consists of rodents (a fraction)
PT = proportion of rodents in the diet that are treated (a fraction)
C = concentration of brodifacoum in treated rodents (mg/kg)

The food ingestion rate, FIR, is estimated using Equation 2.

Equation 2

$$FIR = FMR/(GE \times AE \times M \times Wt)$$

where

FMR = field metabolic rate (kJ/d)
GE = gross energy content of food (kJ/g dry wt)

AE = assimilation efficiency (a fraction)
M = moisture content of food (a fraction)
Wt = animal's body weight (g)

The field metabolic rate (FMR) of each focal species, defined as "the total daily energy requirement for an animal in the wild," was estimated using an allometric equation based on body weight (Equation 3).

Equation 3

$$FMR = a \times Wt^{b}$$

where log(a) and b are the intercept and slope of an allometric regression. From FMR measurements in a wide variety of birds and mammals, Nagy (1987) derived allometric relationships for different animal groups including non-herbivorous mammals and non-passerine birds. The resulting regression statistics are tabulated in the Wildlife Exposure Factors Handbook (WEFH, U.S. EPA 1993).

Note: In the implementation of the daily dose model, Equation 2 and Equation 3 were combined: FIR = $10^{\log(a)}$ x $Wt^{(b-1)}$ / (GE x AE x M).

The following section describes each of the model's input parameters in greater detail.

3.2.2 Input parameters

3.2.2.1 log(a) and b

The allometric parameters log(a) and b were represented in the Daily Dose model by normal distributions, with means and standard deviations taken from the WEFH (U.S. EPA 1993). The mean and standard deviation values for each species, and the sources of those values, are shown in Table 1. For the three mammal species, all values were taken from the empirical regressions for FMR of non-herbivorous mammals. For the two bird species, the mean and standard error for log(a) were taken from the regressions for non-passerines. The values for the regression slope (b) for the birds were taken from regressions for Basal Metabolic Rate (BMR) for Falconiformes (red-tailed hawk) and Strigiformes (great horned owl). The slopes of BMR regressions were used rather than slopes of FMR regressions because for a given taxonomic group the two slopes are not significantly different (U.S. EPA 1993) and the available regressions for BMR were more taxonomically specific (Falconiformes and Strigiformes) than for FMR (all non-passerines combined).

3.2.2.2 Wt (body weight)

Data on body weights of coyote, kit fox, and great horned owl were taken from the Cal/Ecotox database (California EPA 2003). Data for red fox and red-tailed hawk were taken from the WEFH (U.S. EPA 1993). For coyote, red fox, kit fox, and great horned owl we used the mean and standard deviation (calculated from the reported standard error and number of

observations) from the study that reported the smallest mean adult body weight (Windberg et al. 1997 for coyote, Storm and Ables 1966 for red fox, O'Farrell and Gilbertson 1986 for kit fox, and Pakpahan et al. 1989 for great horned owl). For red-tailed hawk, the WEFH listed adult weights from three studies, but none included estimates of variance. The results from the three studies were very similar, and in each case males were slightly smaller than females. We used the mean and standard deviation of the three values for male red-tailed hawks in the dietary exposure model. FIR, and consequently dietary exposure, both increase with decreasing body weight. By using the mean and standard deviation from the smallest group in the database, the Wt distribution in the daily dose model was biased toward lower body weights and higher exposure.

Wt was represented in the daily dose model by a lognormal distribution with mean and standard deviation values selected as described above. A lognormal distribution for weight is appropriate because (a) the lognormal distribution is truncated at zero which is consistent with the possible weight values, and (b) body weights for most animal populations generally follow a lognormal shape with the largest percentage of animals having similar weights and a small fraction of the population having much larger weight values.

3.2.2.3 GE (gross energy), AE (assimilation efficiency), M (moisture)

GE, AE, and M were represented as constants in the daily dose model. Values for these parameters for a variety of food types and consumers are tabulated in the WEFH (U.S. EPA 1993). The daily dose model used a constant GE value of 20.9 kJ/g for mice, voles and rabbits, from Table 4.1 in the WEFH. The value of AE shown in Table 4.3 of the WEFH is 0.84 for mammals feeding on mammals and 0.78 for birds of prey feeding on mammals. Because food energy content (GE) is reported in dry weight units, it must be converted to wet weight based on the moisture content of the food. The model assumed a moisture content of 68%, which is the value shown for mice, voles, and rabbits (WEFH Table 4.1). Together, these three parameters convert the daily energy requirement (field metabolic rate, FMR, in kJ/d) to an equivalent daily food requirement (food ingestion rate, FIR, in kg wet weight/kg body weight/d).

3.2.2.4 PD (proportion of rodents in diet)

The WEFH (U.S. EPA 1993) and the Cal/Ecotox Exposure Factor tables (California EPA 2003) summarize data on dietary composition from studies based on stomach analysis, scat analysis (for mammals), pellet analysis (for birds), and visual observations of prey captured or prey remains found in nests. In most cases, we obtained the original publications cited in the tables and extracted information about the habitat, geographical location, landscape, season, and analytical methods used in each study. Some publications reported results by month or by season, and a few compared diets in different habitats. Most also listed the species of rodents observed in the diet (Table 2).

Because PD represents the percentage (by weight) of rodents in the diet, only data that reflected percentage of rodents in the total diet were used in the exposure model. We did not use observations from studies that reported only the percentage of stomachs, scats, or pellets

that contained rodent remains. In some cases it was not clear whether the values reported represented percentage of rodents in the diet, or percentage of stomachs/scats/pellets that contained rodents. In these cases, if the total of the values reported for all diet items equaled 100%, it was assumed that the values represented percentage in diet. Some studies reported percentages in terms of biomass (wet or dry weight) of prey, corresponding directly to the meaning of PD. Others reported percentages of prey volume or prey numbers. Such values were accepted as surrogates for percentage of biomass, with the recognition that this introduced some error into the representation of PD.

Very few of the publications presented data for individual predators. Generally, the available data were average values representing many sources of variation (e.g., between individuals, between populations, variation in space or time). The available data generally did not represent the variation in diet among individuals within a local population at a particular time, or variation from day to day in the diet of an individual animal.

Nearly all the studies were conducted in rural or wild habitats. The field data were therefore too limited to support generalizations about differences in PD between rural, urban, and suburban environments. For this reason, our original intention of conducting separate analyses for the three types of habitat was considered beyond what the existing data would support. The model could be used to explore the implications of different assumptions about the diets of predators and scavengers in urban and suburban habitats, but we did not attempt to do this.

The data used in estimating PD for the exposure model are presented in Appendix A. The number of observations ranged from 11 for great horned owl to 98 for coyote. The distributions of PD for each species are shown in Figure 3. For each focal species, the parameters of a beta distribution were derived using the Crystal Ball distribution fitting routines. All reported PD values were given equal weight in the data used to derive the beta distribution parameters, although they may have represented different sample sizes, sampling periods, sampling areas, and sampling techniques.

Although the fitted PD distributions did not strictly represent variation among individuals, in the daily dose model they were used to represent variation among individuals. The simulated "individuals" in the daily dose model reflected a composite of the individuals from all the populations represented in the database. This may have overestimated the variability of PD among individuals within a single local population. Many predators, including the five focal species we modeled, are opportunistic, and their diet reflects available food supply. In relatively simple or homogeneous environments, diets are probably more similar among individuals than in complex habitats where a wider variety of food can be found.

While the overall PD for an individual was drawn from the beta distributions described above, each individual's diet was assumed to vary from day to day. The percentage of rodents in an individual's diet on a single day was represented in the daily dose model by the variable DPD (Daily PD). Variation in DPD for each daily simulation (inner loop iteration, as discussed below) was represented by a lognormal distribution with a mean (a time-invariant property of the individual) drawn from the overall PD distribution (beta) and a standard

deviation of 5. The lognormal model was selected for DPD because it includes only positive values and seems a reasonable choice. No data were available for direct assessment of possible distributions. A sensitivity analysis in which the magnitude of the standard deviation was varied from 3 to 10 (see Section 3.4.3.2) indicated little or no effect on the model predictions.

3.2.2.5 PT (proportion of rodents exposed to brodifacoum)

We were unable to find any data regarding the proportion of rodents in the environment or in a predator's diet that may be exposed to rodenticides. Considering the variety and abundance of small and medium-sized rodents available to the focal species in most habitats, the proportion of exposed rats and mice in the diet of most individuals is likely to be quite small. The food species listed in the dietary analysis studies described above (Table 2) included a variety of rodents, especially voles, mice, and squirrels. Cotton rats, wood rats, and kangaroo rats appeared on diet inventories from several studies. Norway rats and house mice were observed occasionally in the diets of coyote, red fox, red-tailed hawk, and great horned owl (Table 3). In the studies where Norway rats and house mice were reported (7 observations out of approximately 160 listed in Appendix A), they comprised only 0.3% to 17.8% of the rodents in the diet.

The proportion of Norway rats and house mice that are exposed to a brodifacoum baiting program is unknown, but is likely to be much smaller than one in ten. It is likely that exposed rodents are more susceptible to predation than unexposed rodents, so the proportion of exposed rodents in a predator's diet may be greater than the proportion of exposed rodents in the environment overall. In the absence of data to support any particular value of PT, we compared results of the daily dose model using PT values ranging from 1% to 15%. The dietary composition data reviewed above suggest that even the lowest of these values is probably an overestimate.

The long-term PT was assumed constant for each individual and identical for all individuals in a model run, reflecting the characteristics of the potential prey populations in a local environment. However, whether or not an individual predator actually encountered an exposed rodent on a given day was considered a matter of chance. The percentage of exposed rodents on a single day was represented in the daily dose model by the variable DPT (Daily PT). Because a single rat would represent a substantial fraction of the daily food intake of an individual predator, intermediate values of DPT would be unlikely; that is, the day's rodent intake would be either entirely exposed or entirely unexposed. The inner loop (discussed below) of the daily dose model assumed that a predator eating an exposed rodent would have a DPT of 1 for that day, and a predator not eating an exposed rodent would have a DPT of 0 for that day. To simulate the day to day occurrences of exposed rodents in an individual's diet, we assumed that an individual with an overall PT of X% (the value assigned to the PT parameter in the outer loop of the model) would eat no unexposed rodents (i.e., DPT = 1) on X% of the days, and no exposed rodents (i.e., DPT = 0) on 100-X% of the days. This assumption was represented in Crystal Ball by a binomial distribution for DPT with p = PT, trials = 1.

3.2.2.6 C (concentration of brodifacoum in treated rodents)

The model assumed that, if the diet of an individual predator on a given day includes exposed rodents (as determined by PD and PT) then those rodents are selected at random from the population represented by the residue concentrations, C, measured in field studies. Data on brodifacoum concentrations in rodent carcasses and live rodents collected during baiting programs were obtained from industry-sponsored field studies (Koubek 1980; Edwards and Swaine 1983; Edwards et al. 1984a; Edwards et al. 1984b) and other sources (Merson et al. 1984; Howald et al. 1999). The measured concentrations from rat control studies (data from a vole control study were not used) are listed in Table 4. Most of the data were for commensal and field uses on farms. Values were reported as mg brodifacoum per kg body weight. Where the level of brodifacoum in a carcass was reported as less than the limit of detection (LOD) or limit of quantification (LOQ), the reported LOD or LOQ was used.

The most complete exposure data came from three studies (Edwards and Swaine 1983; Edwards et al. 1984a; Edwards et al. 1984b) that investigated the hazard to non-target animals from the use of grain baits and wax-block baits (either "saturation" or "pulsed" baiting). The majority of the baiting was concentrated around buildings, but a few bait areas included fields, a rat-infested portion baited away from a farm building, hedgerows, woods, rough ground, or a haystack. Some of the farms that were given instructions for pulsed baiting did not follow the rules and baiting was essentially saturation. A total of 144 rats found dead above ground were analyzed for brodifacoum residues. In one study (Edwards et al. 1984a), other rodents (5 house mice, 4 wood mice, and 1 vole) found dead above ground were also analyzed. Also, 20 rats were trapped, killed, and analyzed for brodifacoum residues; these results were not included in the distribution analysis.

Koubec (1980) reported brodifacoum residue data for 7 individual rats, three from a hog farm trial and four from a sewer trial. The rodents were "found dead, moribund or were killed in the region of the bait stations." Since the data for carcasses were not distinguished from those for live rats, and since only a small number of rats were analyzed, these data were not included in the modeled distributions. The other studies cited used broadcast application of brodifacoum, which is not representative of commensal use. The data from these studies also were excluded from the analysis.

The data from the three central studies (Edwards and Swaine 1983; Edwards et al. 1984a; Edwards et al. 1984b) were analyzed to determine whether concentrations in carcasses were affected by baiting practices (saturation vs pulsed baiting), formulation (pellets vs wax blocks), and other experimental factors. The results from analysis of variance and nonparametric hypothesis testing indicated that no significant differences were evident among the data from the three studies, and the data for all rodent carcasses (including the small number of mice and voles) were pooled (Figure 4). C was represented in the daily dose model by a beta distribution fitted to the data in Crystal Ball (alpha = 0.701, beta = 9.401, scale = 26.26).

The model assumed that the distribution fitted to the available field data for C applied to all exposed rodents in the diet of every coyote, regardless of baiting practices, rodent density, or other factors. Use of carcass residues overestimated exposure to predators, because

brodifacoum concentrations in live rats were lower on average than concentrations in carcasses (Table 4). This is a point where the model could be adapted to represent various scenarios and assumptions.

3.2.3 Model implementation

The daily dose model was implemented as a 2-dimensional Monte Carlo analysis in Crystal Ball (Figure 5). The outer loop of the model represented variation in food ingestion rate and overall diet among individual predators. The inner loop represented variation in the day to day dietary dose to an individual. In each iteration of the outer loop, values were selected from the distributions for log(a), b, Wt, and PD, representing the (assumed time-invariant) characteristics of an individual predator in a particular habitat. In each iteration of the inner loop, values were selected from the distributions for DPD, DPT, and C. To summarize the information presented in Section 3.2.2, the DPD distribution was assumed to be lognormal with mean = PD (selected in the outer loop) and standard deviation = 5; the DPT distribution was a binary distribution with p = PT (defined as a constant in the outer loop) and trials = 1; and the C distribution was a beta distribution fitted to field data.

The simulation was run with 100 iterations of the outer loop (representing 100 individuals) and 1000 iterations of the inner loop (representing 1000 independent predictions of daily dose to one individual). The model output therefore consisted of 100 distributions, each consisting of 1000 daily dose predictions. These data were used to set the parameters of the input distributions in the cumulative dose model, as described below.

3.3 Stage 2. Cumulative Dose Model

3.3.1 Model equations

The cumulative dose model was based on simple uptake and depuration equations:

Equation 4

$$CA_i = CB_i + DD_i$$

Equation 5

$$CB_i = CA_{i-1} \times e^{-k(t_i - t_{i-1})}$$

where

CB_i = concentration in predatory before feeding event *i* (mg/kg)
CA_i = concentration in predator after feeding event *i* (mg/kg)
DD_i = daily dose from feeding event *i* (mg/kg)

k = depuration constant = ln(2)/halflife (d^{-1})
t_i = time (days) of feeding event *i*

Note: In this implementation of the model, the time interval between feeding events is always 1 day, so $t_i - t_{i-1}$ is always 1.

3.3.2 Input parameters

3.3.2.1 DD (daily dose)

Each individual predator was assumed to receive a dose of brodifacoum (or no brodifacoum, i.e., a dose of zero) on each day of the simulation. For each individual, the dose on a single day was selected from a lognormal distribution whose mean and standard deviation were those defined for the individual as described below. The kernel of the cumulative dose model generated 90 independent estimates of daily dose for that individual, and assumed that the 90 random daily dose values occurred in a daily sequence (DD_1 through DD_{90}), representing daily inputs to the simple uptake-depuration calculations represented in Equation 4 and Equation 5.

The mean DD for each individual was selected from the DD Mean distribution generated in the daily dose model. The coefficient of variation for each individual (representing day to day variation in dose) was selected from the DD CV distribution generated in the daily dose model. The standard deviation for each individual was calculated as the mean times the coefficient of variation. For an individual on any given day, the probability of a particular dose was assumed to follow a lognormal distribution. Viewed in another way, it was assumed that a series of independent daily doses to an individual would fit a lognormal distribution.

The output from a representative run of the daily dose model was used for an exploration of the assumptions about DD Mean and DD CV distributions. On statistical theoretical grounds, the mean of a lognormal distribution is expected to have a beta distribution, and the CV of a lognormal distribution is expected to have a gamma distribution (Berger 1980). Alternatively, lognormal distributions might be appropriate for DD Mean and DD CV. We compared various distributions for mean and CV, using the resulting DD distributions as the basis for comparison. The DD distributions were practically identical whether DD Mean and DD CV had beta and gamma distributions, lognormal distributions, or Crystal Ball's best fit distributions. We therefore assumed the theoretically-based beta and gamma distributions for DD Mean and DD CV, respectively, in the cumulative dose model. The DD Mean and DD CV distributions were derived in Crystal Ball by processing the output of each run of the daily dose model, fitting beta and gamma models to the means and CVs of the DD distributions generated by the daily dose model. Each cumulative dose model run was therefore based on a specific daily dose model run, and incorporated all the assumptions (e.g., values of PD, PT, and C) in that daily dose model run.

3.3.2.2 *k* (depuration constant)

In the cumulative dose model, the depuration process was represented as a first-order process (Equation 5) characterized by the rate constant k (k = ln(2)/halflife). As discussed in the Problem Formulation (Section 2.3.3), this was a simplification of the actual depuration kinetics, and we recognized that this introduced some uncertainty into the analysis.

Halflife was set as a constant for all individuals and all days in each run of the cumulative dose model. Because the first-order model was a simplistic approximation of the actual depuration process, it was difficult to judge what would be the most appropriate value for halflife. We tested the sensitivity of the cumulative dose model to the assumed halflife by running it with halflife values ranging from 2 to 200 days.

3.3.2.3 CB (concentration before feeding), CA (concentration after feeding)

For each 90-day simulation sequence, the concentration of brodifacoum in the predator before the first feeding (CB_1) was assumed to be zero, and the concentration after the first feeding (CA_1) was equal to that day's daily dose (DD_1). Feedings were assumed to take place exactly one day apart. The brodifacoum concentration in the predator was assumed to decline between feedings according to the first-order equation described above. Thus the concentration before the second feeding (CB_2) was calculated as shown in Equation 5. To this was added the second day's daily dose (DD_2) to estimate the concentration after the second feeding (CA_2) as shown in Equation 4. These calculations were repeated through 90 days. The concentration of brodifacoum in the predator after feeding varied over time depending on the dose and timing of each exposure, and the highest concentration reached during the 90-day simulation (maximum of CA_1, CA_2, …CA_{90}) was recorded as the key output parameter.

3.3.3 Model implementation

The cumulative dose model was implemented as a 2D simulation in Crystal Ball (Figure 6). In each of the 100 iterations of the outer loop, the mean and coefficient of variation of DD for a single individual were selected at random from lognormal distributions for these variables (DD Mean and DD CV) as described above. In each of the 100 inner loop iterations, a sequence of 90 independent daily doses was simulated, and a 90-day maximum concentration was calculated. The model output therefore consisted of 100 sets (representing 100 individuals) of 100 simulated 90-d maxima (representing 100 possible outcomes for an individual).

3.4 Results of Exposure Analysis

3.4.1 FMR (field metabolic rate)

The daily dose model for each species calculated FMR by allometry (Equation 3; see Section 3.2.1) and generated a distribution of FMR values (Figure 7). The mean and standard deviation of each FMR distribution are shown in Table 5. The distribution represents variability in FMR among individuals, based on the variability of Wt among individuals and the uncertainty about the estimated allometric parameters.

3.4.2 FIR (food ingestion rate)

The daily dose model for each species calculated FIR using Equation 2 (Section 3.2.1) and generated a distribution of FIR values (Figure 8). The mean and standard deviation of each FIR distribution are shown in Table 5. Because the gross energy content of the food (GE), assimilation efficiency (AE), and moisture content (M) were represented as constants in the model, the resulting variability in FIR among individuals was due entirely to variability in the factors affecting FMR (i.e., the allometric parameters and individual body weight). In a sensitivity run with coyote, Crystal Ball reported that 72.5% of the variance in FIR was due to the allometric parameter b, 23.6% was due to log(a), and 3.9% was due to Wt. Thus the uncertainty in the allometric parameters was the major source of variability in FIR.

The wildlife exposure factor tables (U.S. EPA 1993; California EPA 2003) include data on FIR reported from studies with each of the focal species (Table 6). The reporting units varied widely among these studies, and most of the data required conversion based on assumptions about body weight or the percent moisture of the food, as noted in Table 6. Except for one study with coyote (Huegel and Rongstad 1985), all of the reported measurements were made on animals in outdoor captivity or in the laboratory, where food ingestion was probably less than in the field. The means of the estimated FIR for each species were near the upper limit of the measured FIR values (Table 5).

3.4.3 DD (daily dose)

The daily dose model calculated DD using Equation 1 (Section 3.2.1). Each model run generated probability curves for daily dose for each of 100 individuals. The probability curve for each individual was based on 1,000 daily dose simulations. The day-to-day variation in an individual's diet was repesented by the variable DPD (daily PD), drawn from a lognormal distribution with mean equal to that individual's overall PD and a standard deviation of 5 (an assumed value; sensitivity runs using standard deviation of 3 or 10 were also conducted, as reported below).

PT was constant for each run, with values ranging from 0.01 to 0.15. The day-to-day variation in PT in an individual's diet was represented by a binomial distribution (daily PT either 0 or 1), with the likelihood of PT = 1 on a given day equal to the overall PT for the model run. The input and output parameters of the daily dose model runs are summarized in Table 7.

Because PD and PT varied from day to day for an individual predator, and C varied at random among brodifacoum-treated rodents, the daily dose of brodifacoum to the individual also varied from day to day. The daily dose model (in its inner loop) calculated the dose to an individual 1,000 times, representing 1,000 random combinations of PD, PT, and C. The result was a distribution of 1,000 possible DD values for the individual. Various descriptive statistics were calculated for the distribution, such as the mean, median, and CV of the 1,000 values.

Having determined the DD distribution for one individual, the daily dose model then repeated the process (in its outer loop) for a total of 100 individuals. The individuals differed from each other in FIR (assumed constant for each individual, not varying day to day; see Section 3.4.2) and overall PD. The final output of the daily dose model was therefore 100 distributions (one distribution for each of 100 individuals), as well as 100 values of the distribution means, medians, CVs, and other statistics.

Using Crystal Ball to fit different distribution models to the data, we found that the DD distribution for a given individual was typically lognormal (see Section 3.3.2). Each individual's DD distribution was defined by its mean and CV (CV was assumed to be independent of the mean). Theoretically, the means of a lognormal distribution are themselves described by a beta distribution, and the CVs by a gamma distribution. Both theoretical assumptions were confirmed by Crystal Ball for the DD Mean and DD CV distributions. The distribution of means reflects variation in daily dose among individuals, while each CV measures the random day-to-day differences in one individual's dose. Taken together, the distributions of means and CVs constituted a complete representation of the output of a daily dose model run, and were passed as input variables to the cumulative dose model (Section 3.3.2).

3.4.3.1 Influence of PT

A series of model runs were conducted to explore the sensitivity of the daily dose model to variation in PT, using coyote as a test case. The resulting daily dose distributions increased with increasing PT (Table 7, Figure 9). The change in DD was approximately proportional to the change in PT. The daily dose model was therefore very sensitive to the assumed value of PT. Based on the considerations presented in Section 3.2.2, we believe that in most cases PT is likely to be less than 0.01 (fewer than 1% of all rodents in the diet have been exposed to brodifacoum), the lowest value used in our simulations. Circumstances in which PT is greater will result in proportionally greater daily doses. Increasing PT also was accompanied by decreasing day-to-day variability in the daily dose to an individual (Table 7).

3.4.3.2 Influence of daily PD variability

The model assumed that the day-to-day variation in PD around an individual's overall average PD was described by a lognormal distribution with a standard deviation of 5. One coyote model run (with PT = 0.025) was repeated with the daily PD standard deviation set to 3 and 10. The DD mean and DD CV were unaffected (Table 7), but the DD distribution included more extreme values with a standard deviation of 10 and fewer extreme values with a standard deviation of 3 (Figure 10). The value of 5 was adopted for all other daily dose model runs.

3.4.3.3 Comparison among species

The distributions of 100 individual DD means for coyote, red fox, kit fox, red-tailed hawk, and great horned owl are compared in Figure 11. For most individuals the DD mean was near the lower end of the range for the species, but for 5 to 10% of the individuals the DD means were considerably greater than the others, represented by the tail extending to the right of each distribution. The distributions based on PT = 0.025 were proportionately greater than the distributions based on PT = 0.01 for all species, as had been found with coyote (Figure 9). Daily doses were smallest for coyote and red fox, slightly greater for red-tailed hawk, and greatest for kit fox and great horned owl. The differences among species in daily dose were most consistent with the differences in PD (Table 7). FIR (Table 5) had a secondary influence, particularly in the case of the red-tailed hawk: despite the hawk's greater use of rodents, its low FIR resulted in a daily dose only slightly greater than those of coyote and red fox.

3.4.4 Cumulative dose

The distributions of DD Mean and DD CV from the output of the daily dose model were imported to the cumulative dose model. The cumulative dose model drew from the DD Mean and DD CV distributions to select parameters for the DD distribution for each of 100 individuals. From these parameters, a 90-d series of DD values was generated for each individual. The cumulative dose to the individual from the 90-d series was estimated using an uptake - depuration model (Equation 4 and Equation 5), and the highest dose occurring during the 90-d period was determined. This 90-d simulation was performed a total of 100 times for each individual. The mean of the 100 simulation outcomes was calculated, and the 100 means (from 100 individuals) were plotted as reverse cumulative frequency distributions.

3.4.4.1 Influence of halflife

As discussed in Section 3.3.2, the first-order depuration model we used was a simplified representation of the depuration process observed for brodifacoum in rats. When a rat ingests a dose of brodifacoum, concentrations in the rat's body decline quickly at first, then more slowly. The initial halflife may be on the order of 2 to 5 days, while the halflife of the second phase halflife may be 100 to 200 days. To observe the influence of halflife on the 90-d maximum concentration, we conducted a series of cumulative dose runs based on the output of the daily dose model for coyote. These model runs used halflives of 2, 5, 10, 20, 50, 100,

or 200 days. Differences between the resulting cumulative dose distributions (Figure 12) appeared to be greatest around the 0.1 exceedence level (the 90th percentile of the distributions). Varying the halflife from 2 d to 200 d resulted in about a 2-fold increase in cumulative dose at PT = 0.01 and PT = 0.025 and a 3-fold increase at PT = 0.1 (Table 8). These differences were relatively small compared to differences due to PT (Figure 13) and differences among species (Figure 14). We adopted 50 d as the standard value for halflife in the cumulative dose model. Dose distributions generated using the 50-d halflife were similar to those generated using 100-d and 200-d halflives (Table 8, Figure 12).

3.4.4.2 Influence of PT

The consequences of different assumptions about PT were explored in a series of cumulative dose model runs with coyote. As discussed above (Section 3.2.2) we believe the actual value of PT under most circumstances is less than 0.01. We generated cumulative dose distributions based on daily dose model runs with PT = 0.01, 0.025, 0.05, 0.075, 0.10, and 0.15. Increasing PT from 0.01 to 0.025 resulted in a 2-fold increase in 90-d maximum dose, while increasing PT to 0.15 resulted in a 10-fold increase in cumulative dose (Table 9, Figure 13). These runs all assumed a 50-d halflife.

3.4.4.3 Extended simulation period

The choice of a 90-d simulation period — one season — was a practical decision made during model scoping. To investigate the behavior of the cumulative dose model over longer periods, we performed three runs with coyote for 180 d and 360 d. With halflives of 5 or 50 d, extending the simulation to 360 d resulted in about a 2-fold increase in the maximum cumulative dose, compared with a 90-d run (Table 10). With a 200-d halflife, the maximum cumulative dose increased about 3-fold.

3.4.4.4 Comparison among species

The cumulative dose model was run using daily dose output for coyote, red fox, kit fox, red-tailed hawk, and great horned owl, assuming a 50-d halflife. The cumulative dose distributions (Figure 14) mirrored the daily dose distributions (Figure 11). Cumulative exposure was greatest for kit fox and great horned owl, and least for coyote and red fox. The 90th percentiles (10% exceedence values) for cumulative dose ranged from 0.04 mg/kg for coyote and red fox to 0.10-0.12 mg/kg for kit fox and great horned owl (Table 11). For all species, cumulative dose was about twice as great with PT = 0.025 as with PT = 0.01.

4 Effects Analysis

The effects analysis was based on laboratory toxicity studies. As discussed in Section 2.3.4, only studies generating toxicity results in terms of dose to the animal (e.g., LD50) were used; studies generating results in terms of concentration in the diet (e.g., LC50) were not used.

4.1 Data Collection and Evaluation

4.1.1 Mammalian data

Mammalian toxicity data from the following references were reviewed for use in the risk assessment: Hadler 1974b, a, 1975c, a; Parkinson 1976, 1978; Godfrey et al. 1981b, a; Godfrey 1984; Godfrey et al. 1985; O'Brien and Lukins 1990; Duerden 1993.

The following mammalian effects data were modified or excluded:

- Godfrey et al (1981a), dogs – trials 1 and 2 were combined.
- Godfrey (1984), wallaby – trials 1 and 2 were combined.
- Godfrey et al. (1981b), and Hadler (1975c), rabbits – studies were combined.
- Hadler (1974b), Parkinson (1978), and Duerden (1993), rats – all trials and studies were combined.
- Parkinson (1976), dogs and cats – data excluded for both dogs and cats due to insufficient numbers of animals tested (n<3).
- Hadler (1975a), guinea pig – trials 1 and 2 were combined.

4.1.2 Avian data

Avian toxicity data from the following references were reviewed for use in the risk assessment: Hadler 1975b; Ross et al. 1977b, a; Ross et al. 1980; Godfrey 1986; Roberts and Fairley 1986.

The following avian effects data were modified or excluded: Godfrey (1986) – all of the data were excluded from trial 1 and 2 with the exception of the ring-necked pheasant and harrier hawk (trial 1) and California quail and pukeko (trial 2) due to lack of dose-response (generally most or all the birds survived or died at all dose levels). In the case of the pukeko the more conservative trial (trial 2) was used.

4.2 Non-Target Species Effects Models

For the acute toxicity studies used in this risk assessment, the response variable is binary: the test animal is either dead or alive at the end of the test. The basic model for a mortality test data is the logistic regression:

Equation 6

$$Y_{jk} \sim \text{binomial}(p_{jk}, n_{jk})$$

where j represents a species-specific test, y_{jk} is the number of dead test animals at dose level k, p_{jk} is the long-term average expected mortality rate, and n_{jk} is the number of test organisms used in the kth dose level. The p_{jk} is the probability that any animal will be killed at dose level D_{jk}, and is linked to the toxicant dose by a linear model:

Equation 7

$$\text{logit}(p_{jk}) = \alpha_j + \beta_j \log(D_{jk})$$

where α_j and β_j are the regression coefficients to be estimated for each test, D_k is the kth dose level, and the logit function is: $\text{logit}(p_{jk}) = \log([p_{jk}/(1-p_{jk})])$.

The objective of the modeling is to estimate the regression coefficients α_j and β_j from which an LD_{50} is estimated. The LD_{50} is the dose level corresponding to $p_{50} = 0.5$ (and $\text{logit}(p_{50}) = \log(0.5/(1-0.5))=0$). Equation 7 results in:

Equation 8

$$LD_{50} = \exp\left(-\frac{\alpha_j}{\beta_j}\right)$$

A Bayesian hierarchical modeling framework was used to evaluate the effects data for each species. Hierarchical models reduce the effect of incomplete data sets, small numbers of tests, inconsistent information on effects among species, and other issues that lend uncertainty to the effects models.

Dose-response models were fit individually for each species within the avain and mammalian groupings. Sources of uncertainty inherent in these models include differences among the species-specific responses and the uncertainty about model parameters. In the hierarchical framework, differences among species can be treated as the result of another "super" distribution. The dose-response curves for individual species can be treated as samples from a distribution at a higher level, with each individual dose-response curve representing a random realization from this super distribution.

In this framework, the model parameters (α_j and β_j) associated with test j are assumed to have a normal distribution, with associated hyperparameters:

$$\beta_j \sim N(\beta_{super}, \lambda_1)$$
$$\alpha_j \sim N(\alpha_{super}, \lambda_2)$$

Each of the hyperparameters is modeled as a noninformative prior:

$$\beta_{super} \sim N(0, \lambda_3)$$
$$\alpha_{super} \sim N(0, \lambda_4)$$

$$\lambda_{1,2} \sim G(.01,.01)$$

(Note: N represents the normal distribution and G represents a gamma distribution. These distributions are typical for models and parameters of this type. Also note that λ_3 and λ_4 are precision statistics, or inverse variance statistics, and are therefore set to very small values.) Under this hierarchical model, the joint posterior distribution of all parameters can be expressed as the product of the probability density functions at the different levels:

Equation 9

$$\pi(\beta,\alpha,\beta_{super},\alpha_{super},\lambda_1,\lambda_2 \mid Y) = \pi(Y \mid \alpha,\beta,\lambda_1,\lambda_2)\times \pi(\alpha,\beta,\lambda_1,\lambda_2 \mid \beta_{super},\alpha_{super})\pi(\beta_{super})\pi(\alpha_{super})\pi(\lambda_1)\pi(\lambda_2)$$

From this joint distribution, it is possible to integrate out coefficients and parameters at selected levels to summarize information at a given level. For example, integrating over the species-specific coefficients results in the posterior distribution of the parameters for β_{super} and α_{super}, representing information from all species.

The upper and lower percentiles of the integrated species-specific distributions are generated by calculating the probability of a response conditional on the dose:

Equation 10

$$p(y_k \mid D_{jk}) \propto \iint (y_{jk} \mid \alpha_j,\beta_j,D_{jk})\,\pi(\alpha_j)\,\pi(\beta_j) d\alpha_j\,\beta_j$$

This conditional distribution is then used to generate the posterior limits such that $P(y)<0.05$ and $p(y)<0.90$ for a given dose. Standard numerical approaches are used to draw these values for specific dose levels. The advantage of the above approach is that the correlation among the regression parameters is inherently included in the resulting distribution.

The WinBUGS software system (Spiegelhalter et al. 2000) was used to solve the Bayesian equations. These solutions result in posterior distributions of the random parameters for the species-specific models, the joint distribution across species model, and the upper and lower 10^{th} percentiles of the joint distribution. The outputs are presented in both graphical and tabular form. WinBUGS uses Markov Chain Monte Carlo (MCMC) techniques to solve the integrals found in Bayes' theorem, conditional on the distributional form of the parameters. To run WinBUGS, the user supplies: (1) the model form, (2) the distributional form of all random parameters at each level of the hierarchical model, (3) prior distributions of the parameters, and (4) any calculations involving the random parameters that the user wants the computer to generate. The software system uses random sampling of the conditional distributions to solve Bayes' theorem, resulting in the posterior distribution of the random parameters, conditional on the data. The user can output sufficient statistics of the random parameters at any point in the model hierarchy. Details on the MCMC approach for solving the Bayesian equations are given in Congdon (2001) and Gilks *et al*. (1996).

4.3 Model Outputs

Table 12 presents the model parameters and LD50s associated with the species-specific mammalian models. Table 13 presents this information for the avian models. Figure 15 presents the effects curves for each mammalian species, the median integrated effects curve, and the upper and lower 10^{th} percentile curves. Figure 16 presents the same graphics for the avian data.

The dose-response curve for the 1986 pheasant study was much different in shape from the other studies (Figure 16). A sensitivity analysis demonstrated that removal of this test would have only a small effect on the integrated avian effects curves. For example, the LD50 for the integrated model including the 1986 pheasant study was 3.4 (Table 13), and when the test was excluded from the analysis the LD50 was 3.7. Because the pheasant study met all of the test acceptability criteria outlined in Section 2.3.4, the data were kept in the effects database used in the hierarchical Bayesian modeling.

5 Risk Characterization

5.1 Methods

Risk curves were generated by integrating exposure and effects distributions. The exposure distributions were derived from the cumulative dose distributions described in Section 3.4.4. For each cumulative dose model run, the full set of 10,000 dose estimates (100 estimates for each of 100 individuals) was combined into a single exposure distribution reflecting both within-individual and among-individual variation. The effects distributions were the integrated high-sensitivity, median, and low-sensitivity dose-response curves described in Section 4.3.

If Y_k is a species-specific mortality rate that is dependent on dose, and $\xi(\theta)$ is the distribution of dose with parameters θ, then risk is the integration

Equation 11

$$p(Y_k) = \int \langle Y_k \,|\, \theta \rangle \xi(\theta) d\theta$$

This equation was solved numerically by first evaluating the dose (k) associated with a specific mortality rate (from the effects model), then querying the exposure distribution to find the likelihood of a cumulative dose larger than k. Plots of the exposure exceedence probability against mortality rate were generated, and statistics from the risk curves were extracted for presentation of the risk results.

5.2 Results

Risk curves for each species are presented in Figure 17 through Figure 21. Each figure includes two plots, representing assumptions of PT = 0.01 and PT = 0.025. Each plot shows three curves, representing assumptions of low, median, or high sensitivity for the surrogate species. Each point on a curve indicates the probability of exceedence (vertical axis) of a particular mortality rate (horizontal axis) under a specified set of assumptions about model parameters.

For example, the risk curve for coyote (Figure 17), PT = 0.025, and high sensitivity indicates a 10% probability of the mortality rate exceeding 18%. Risk curves reflecting the assumption of median sensitivity or low sensitivity are considerably lower than the curves for high sensitivity. As a convenience for comparing risk curves, we tabulated the 10^{th}, 50^{th}, and 90^{th} percentiles from each curve (Table 14). Risk curves for the five surrogate species, assuming high sensitivity for each, are compared in Figure 22. The trends were very similar to those for the cumulative dose distributions (Figure 14). Risk was least for coyote and red fox and only slightly greater for red-tailed hawk. Risk was greatest for kit fox and great horned owl. With PT = 0.01, there was little difference between these two species. However, with PT = 0.025, the risk was greater for kit fox than great horned owl.

The effect of the assumed value for the depuration halflife on risk was examined using the output of a series of cumulative dose model runs with coyote (Section 3.4.4.1, Figure 12). For this species, varying the assumed halflife value from 2 d to 50 d resulted in a small increase in estimated risk, but increasing halflife from 50 d to 200 d had almost no incremental effect on risk (Figure 23, Table 15).

The effect of the value of PT on risk was also estimated, based on another series of cumulative dose model runs with coyote (Section 3.4.4.2). The trends in the resulting risk curves (Figure 24, Table 16) were similar in direction to those for cumulative exposure (Figure 13). However, the effect of PT was greater on the risk curves than on the exposure distributions. Risk to coyote was low with PT = 0.01 (1% of the rodents in the diet have been exposed to brodifacoum), even assuming coyote is a highly sensitive species. However, risk increased sharply with increasing PT. In situations where a high percentage of rodents are exposed to brodifacoum, risk of secondary poisoning may become high even for predators with a relatively low proportion of rodents in their diet.

Overall, the analysis indicated that at PT = 0.01 the risk to coyote, red fox, and red-tailed hawk is low, even if these species are all assumed to be highly sensitive. The same would be inferred for other species of birds and mammals whose dietary composition and metabolism are similar to the coyote, red fox, and red-tailed hawk. Risk is greater for kit fox and great horned owl, and other species with a higher percentage of rodents in their diet. Risk to all species is greater in situations where a higher proportion of rodents have been exposed to brodifacoum. As discussed in Section 2.1, the information contained in the risk curves should be useful to regulators when considering the acceptability of risk.

6 Assumptions, Uncertainties, and Limitations

Any risk assessment is subject to numerous assumptions, uncertainties, and limitations of scope that can affect interpretation of the results. The assumptions, uncertainties, and limitations of this risk assessment have been mentioned throughout the report. This section recapitulates the constraints on the assessment and identifies areas where additional data would be most effective.

6.1 Scope

Decisions were made in the Problem Formulation (Section 2) that limited the scope of the risk assessment. Some of these decisions were based on presumptions about relative risk, and were intended to focus our resources on areas where risk was greatest. Other decisions were forced by scarcity of data. The most significant of these decisions are discussed in the following paragraphs.

Dietary intake was the only exposure pathway included in the assessment. We considered exposure from residues in soil, drinking water, and air to be much less significant than dietary exposure (see Section 2.2.1).

Only secondary exposure was considered (see Section 2.2.1). Primary exposure to non-target bait feeders could not readily be incorporated into the models we used for secondary exposure. Primary exposure was considered of less concern than secondary exposure, and more manageable through refinement of bait station design and placement.

We modeled secondary exposure only through predation or scavenging on brodifacoum-containing rodents (see Section 2.2.1). A variety of invertebrates and small birds may also feed on brodifacoum-containing baits and may constitute another route of dietary exposure for some animals. The risk assessment results, based on consumption of rodents, were not necessarily applicable to small insectivores and scavengers that could receive secondary exposure through bait feeders other than rodents. The dietary exposure model could be used to estimate the risk of secondary exposure through non-rodent food sources, based on the fraction of each food type (e.g. insects, small birds) in the diet of the focal species. However, brodifacoum concentrations in these food types are not known. Additional modeling would be needed to estimate those concentrations, if the model were to be adapted for species exposed through non-rodent food types.

Only approved (labeled) brodifacoum bait uses for commensal rodents in and around structures were considered in the conceptual model (see Section 2.3.1). Rodenticide misuse and abuse were not taken into account. This decision had no impact on the outcome of the assessment, because specific aspects of brodifacoum use were not represented in the risk model. Usage factors may affect the relative abundance of exposed rodents (PT). Usage factors may also affect the frequency distribution of brodifacoum concentrations in exposed rodents (C), which in our model were based on field data. The scope of the risk assessment could be broadened if data on C were obtained under a wider variety of baiting situations.

Indoor uses were not explicitly represented in the model (see Section 2.3.1). In terms of the model, indoor use would be expected to reduce PT (because fewer exposed rodents would be present outdoors), thereby reducing the risk from secondary exposure, compared with outdoor uses.

The model was based on a homogeneous spatial-temporal framework; values for model parameters did not vary as a function of time or space. The amount of brodifacoum ingested in one daily feeding event (a function of C and daily values for PD and PT) was independent of other feeding events for the same individual. Seasonal variation was not modeled. For some of the focal species, sufficient dietary composition data may exist to estimate PD distributions for each season, but we did not carry out those analyses. Seasonal differences can also be expected for PT, but data have not been obtained on seasonal variation of factors that would influence PT, such as rodenticide use patterns and rodent population densities.

Short-term variation in exposure, such as would occur during the course of a baiting program at a single site, also was not explicitly represented in the model. With potential baiting sites distributed across the landscape, the feeding range of an individual predator is likely to include baiting programs in different phases, thus dampening the short-term temporal fluctuations that may occur at a single site.

The spatial scale of the model was indeterminate. The landscape-based conceptual framework implied in Figure 2 was not represented spatially in the model; none of the model parameters had a spatial dimension. Spatial variability would be one source of day-to-day variation in an individual's PD and PT, but we did not calculate or estimate how much of the variation in daily PD and PT was attributable to spatial variability, temporal variability, and stochasticity.

The model did not distinguish between urban, suburban, and rural habitats (see Section 2.3.1). The dietary preferences of predators and scavengers, the distribution and density of exposed prey and alternative prey, and the size of feeding ranges would be expected to differ among habitats. Nearly all of the dietary data used in the model were from studies in rural habitats, as were the field data on brodifacoum concentrations in rodents. We ran the model using the available data, which therefore reflected primarily rural conditions. To estimate risk for urban and suburban habitats, assumptions would be needed about habitat-specific differences in FIR, C, PD, and PT.

The effects analysis was based on data for acute mortality, not sublethal or chronic effects (see Section 2.2.3).

The model has not yet been applied to a species that feeds mainly on carrion. Our surrogate species (Section 2.3.2) were opportunistic omnivores, feeding mainly on live prey but also carrion when available. The data on dietary composition of the surrogate species typically include both prey and carrion, usually without distinguishing between them. It should be noted that C was determined only for rats found dead above ground, which had a mean significantly greater than that for live-trapped rodents. Therefore, the risks associated in this

assessment are likely more conservative for true predators and more predictive of true scavengers.

6.2 Daily Dose Model

The allometric model parameters used to estimate FMR were based on empirical regressions for broad groups of birds and mammals (Section 3.2.2.1). The uncertainty in the original allometric parameter estimates was presented in WEFH (U.S. EPA 1993) and the Cal/Ecotox exposure factor tables (California EPA 2003). The daily dose model incorporated this uncertainty into the FMR calculation for each individual. Sensitivity analysis using Crystal Ball indicated that uncertainty about the allometric parameters accounted for most of the variability of FMR estimates (Section 3.4.2).

FMR estimates were less affected by variability in body weight data (Section 3.4.2). The body weight distributions used for each species in the daily dose model were based (with one exception) on the sample distribution from one reported study, and thus reflected variability among individuals in a local population (Section 3.2.2.2). Body weights also vary among populations, but variability among populations was not represented in the daily dose model. Instead, the weight distribution from the study reporting the smallest mean body weight was used.

The model converted FMR to FIR using GE, AE, and M values appropriate for mice, voles, and rabbits (Section 3.2.2.3). For more accuracy, the model would determine the fractional FIR for each food type (based on the weight percentage of that food type in the diet), then sum for all food types. We did not explore this, but for the animals of greatest concern (those with a large fraction of rodents in their diet) the discrepancy would probably be small. The FIR estimates generated by the daily dose model were consistent with the limited available field data (Table 5).

Variability in dietary composition among individuals, and day-to-day variability for each individual, were explicity represented in the daily dose model (Section 3.2.2.4). The variability among individuals was represented by the observed variability in dietary composition among studies reported in WEFH (U.S. EPA 1993) and the Cal/Ecotox exposure factor tables (California EPA 2003). Using data on variability among studies (populations) to represent variability among individuals was a decision forced by the absence of data on individual diets. Most of the dietary composition data were from rural areas, including wildlife reserves, and diets of the same species may be different in urban or suburban habitats. Because the model used distributions that included all observed values that met the selection criteria (Section 3.2.2.4), studies reporting multiple values were more heavily represented in the distributions than studies reporting single values.

The analysis of dietary composition data required conversion from various field measures to estimates of fresh weight in the diet. The relative number, volume, or mass of food remains in pellets, scats, and stomach contents are not necessarily the same as the relative fresh weights of the food items. The percent of food items by numbers, a common reported

measure of dietary composition, overestimates the fresh weight percentage of small food items and underestimates large food items. The magnitude of the discrepancy introduced by equating pellet, scat, and stomach analyses with fresh weight dietary percentages was not explored.

A major source of uncertainty in the daily dose model was the proportion of rodents in the diet that have been exposed to brodifacoum (PT; see Section 3.2.2.5). PT was a key variable in scenario interpretation, yet we found no data to quantify it. The following are some presumptions about PT:

- In a secondary exposure feeding study, PT equals 1. In the immediate vicinity of a structure where baiting is in progress, PT may approach 1.
- In an urban setting, baiting density (placements per unit area) is presumably higher than in a rural setting. But total rodent populations may also be denser in an urban than a rural setting. These trends would have opposing effects on PT, and the result might vary in either direction.
- The likelihood of an individual's home range including a baiting site would increase with increasing home range size. On the other hand, an individual with a larger home range would have access to more unexposed prey than an individual with a smaller home range. The home range of a kit fox is relatively large (1-10 km^2), that of a great horned owl relatively small (0.1-0.5 km^2) (Figure 25). If baiting density were the same in the habitats of both species, the home range of a kit fox would be more likely to include a baiting site than the home range of a great horned owl. However, a kit fox whose home range included a baiting site would have access to more unexposed prey than a great horned owl whose home range included a baiting site.
- Predators might be attracted to a baiting site within their home range, because it would have many rodents (hence the need for chemical control) and because poisoned rodents may be easy prey.

With so many uncertainties about PT, we used professional judgment to estimate the fraction of rodents in a predator's feeding range that might have come in contact with a brodifacoum baiting program. Considering the abundance and variety of rodents available to predators, we concluded that the fraction of exposed rodents in most habitats is much lower than 0.01. Under some circumstances, the fraction could be greater in a localized area. We might picture PT contours on the landscape, with peaks at baiting stations and fewer exposed rodents further from baiting stations. We have no data to quantify this conceptual model.

Finally, the daily dose model was affected by uncertainty and variability of brodifacoum concentrations in rodents (C, see Section 3.2.2.6). The model input for C was a distribution based on data from three field studies. Variability among individuals was reflected in the field data and was represented directly in the model. We did not quantify the contribution of variability in C to the variability of daily dose estimates. Use of data from these three studies introduced uncertainty into the model because the representativeness of the data (relative to other locations and other baiting situations) was unknown.

6.3 Cumulative Dose Model

The cumulative dose model and the dose-response model were based on a simplification of the toxicokinetics of brodifacoum. The models represented the body of the predator as a single compartment, and exposure in both models was expressed as the concentration of brodifacoum in the whole body. We did not attempt to model the transfer of brodifacoum between compartments within the body, such as the liver and blood. Although the complexities of brodifacoum toxicokinetics were not represented in the model, we considered development of a full toxicokinetic model beyond the scope of the risk assessment and also beyond the extent of available data.

The cumulative dose model also simplified the kinetics of brodifacoum depuration. The model assumed that brodifacoum whole body concentrations declined following first order kinetics, while laboratory observations suggest that depuration is typically biphasic (see Section 3.3.2.2). We explored the consequences of this uncertainty by conducting sensitivity analyses using a range of halflife values (Section 3.4.4.1). The depuration rate had a small influence on cumulative dose (Figure 12) and risk (Figure 23).

The cumulative exposure model simulation lasted 90 days. Terminating the simulation at 90 days was a practical decision, intended to correspond to approximately one season in the field. Extending the simulation for longer periods (180 or 360 d) resulted in a 2- to 3-fold increase in maximum cumulative exposure (Section 3.4.4.3, Table 10). We did not carry these exposure estimates forward to determine the effect of the simulation period on risk.

6.4 Effects Analysis

Our analysis of brodifacoum effects was subject to the uncertainties that apply to virtually all ecological risk assessments:

- Representativeness of toxicity test species.
- Relevance of lab tests to field conditions.
- Reliability of toxicity test procedures and results.
- Uncertainty about logistic model parameters.
- Uncertainty about integrated effects model parameters.
- Extrapolation to effects on population abundance.

Of these uncertainties, the one with the greatest influence on the risk estimates was the applicability of data from the toxicity test species to the surrogate species. The estimated risk to each surrogate species was highly dependent on the species' assumed sensitivity (see Figure 17 through Figure 21).

The test species most closely related to the surrogate mammals was the dog. The dog was less sensitive than most of the other mammalian test species, and the dog's dose-response curve was to the right (indicating lower sensitivity) than even the low sensitivity (90^{th} percentile) integrated dose-response curve (Figure 15). Similarly, the test species most

closely related to the surrogate birds was the harrier hawk. The dose-response curve for the harrier hawk was nearly identical to the low-sensitivity integrated curve (Figure 16). If the surrogate species are similar to the dog and the harrier hawk in their sensitivity to brodifacoum, risk calculations based on the assumption of high sensitivity (e.g., Figure 22 through Figure 24) are greatly overestimated.

6.5 Data Gaps

The risk assessment could be refined with additional data, of which the most important are the following:

- Information on baiting practices in urban, suburban, rural habitats. This would include the proportion of houses, farms, warehouses, etc. where baits are used (baiting density); the amount, timing and duration of baiting; bait station design and placement; and practices for removing carcasses and unused bait.

- Brodifacoum toxicity data for additional species of non-target birds and mammals. There is considerable variation in the dose-response curves for different species, and the risk estimates were strongly affected by the assumed sensitivity of the surrogate species. Toxicity data for additional species would improve our estimates of species sensitivity distributions.

- Additional data on concentrations of brodifacoum in target rodents and non-target animals collected during field trials. The scope of the risk assessment could be broadened if data on C were obtained under a wider variety of baiting situations. Rodents would be the primary focus, but other species (including insects, small birds, and rabbits) could also be included.

- Information on the toxicokinetics of brodifacoum in non-target birds and mammals. Researchers in industry and academia are making good progress toward understanding how brodifacoum moves within the body, and how brodifacoum concentrations in different organs and tissues affect clotting time, hemorrhaging, and death. However, data are still insufficient to parameterize even a simple two-compartment (body and liver) kinetic model for the rat. As data become available, the exposure model could be refined to account for brodifacoum concentrations in different internal pools, and the effects model could be refined to account for toxicity in terms of concentrations in specific internal pools, such as the liver.

7 Conclusions

The risk of brodifacoum-induced mortality in coyote, red fox, and red-tailed hawk is low, even if these species are all assumed to be highly sensitive to brodifacoum.

By inference, the same conclusion applies to other species of birds and mammals with similar dietary composition and metabolism.

Risk is slightly greater for species with a higher percentage of rodents in their diet, such as the kit fox and great horned owl.

These risk estimates were strongly influenced by the values assumed for PT, the proportion of rodents in the diet that have been exposed to brodifacoum. In circumstances where a high proportion of the rodents in a predator's foraging range have been exposed to brodifacoum, less susceptible species (such as coyote, red fox, and red-tailed hawk) may be at risk.

These risk estimates were strongly influenced by uncertainty about the sensitivity of the surrogate species to brodifacoum. Without further information about the sensitivity of an untested species, assuming median (or mean) sensitivity would generate a risk estimate for the most likely case. The assumption of high sensitivity would be more protective of other species, regardless of the actual sensitivity of the surrogate species.

Because risk was calculated in terms of probability of individual mortality, the results were directly applicable to survival of individuals of non-target species, which was one of the two assessment endpoints.

The risk assessment did not directly estimate risk to the second assessment endpoint, population abundance of non-target species. Individual mortality, the endpoint of our analysis, is one of many factors determining population dynamics and abundance. Beyond the scope of this risk assessment, population models could be developed for each surrogate species, or for generic predator and scavenger species, to estimate the population-level impact of brodifacoum-related individual mortality.

8 References

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Tables

Table 1. Input parameters for estimation of Field Metabolic Rate by allometry.

	log(a)		b		Wt (g)	
Focal species	Mean	SE[a]	Mean	SE[a]	Mean	SD[b]
Coyote	0.412[1]	0.058[1]	0.862[1]	0.026[1]	9499[2]	3600[2]
Red fox	0.412[1]	0.058[1]	0.862[1]	0.026[1]	3940[3]	1493[4]
Kit fox	0.412[1]	0.058[1]	0.862[1]	0.026[1]	1936[5]	231[5]
Red-tailed hawk	0.681[6]	0.102[6]	0.648[7]	0.037[6]	1063[8]	127[8]
Great horned owl	0.681[6]	0.102[6]	0.690[9]	0.037[6]	1229[10]	212[10]

[a] Standard Error
[b] Standard Deviation

Sources:
[1] Wildlife Exposure Factors Handbook (U.S. EPA 1993), Table 3-4, non-herbivorous mammals
[2] Cal/Ecotox Exposure Factors (California EPA 2003), smallest adults, female, New Mexico
[3] Wildlife Exposure Factors Handbook (U.S. EPA 1993), smallest adults, female, Iowa
[4] Estimated by assuming same coefficient of variation as coyote (37.9%)
[5] Cal/Ecotox Exposure Factors (California EPA 2003), smallest adults, female, California
[6] Wildlife Exposure Factors Handbook (U.S. EPA 1993), Table 3-4, non-passerine birds
[7] Wildlife Exposure Factors Handbook (U.S. EPA 1993), Table 3-2, Falconiformes
[8] Wildlife Exposure Factors Handbook (U.S. EPA 1993), males (smaller than females), three studies
[9] Wildlife Exposure Factors Handbook (U.S. EPA 1993), Table 3-2, Strigiformes
[10] Cal/Ecotox Exposure Factors (California EPA 2003), males (smaller than females)

Table 2. Rodents reported in diets of coyote, red fox, kit fox, red-tailed hawk, and great horned owl.

Taxonomic group[1]	Coyote[2]	Red fox[3]	Kit fox[2]	Red-tailed hawk[3]	Great horned owl[2]
Family Dipodidae (jumping mice, birch mice, jerboas)					X
Zapus (jumping mice)					X
Family Geomyidae (pocket gophers)	X		X	X	X
Thomomys (western pocket gophers)	X		X		
Family Heteromyidae (kangaroo rats, pocket mice)	X		X	X	X
Subfamily Dipodomyinae (kangaroo rats, kangaroo mice)	X		X	X	X
Dipodomys (kangaroo rats)	X		X	X	X
Subfamily Perognathinae (pocket mice)	X		X	X	X
Chaetodipus (coarse-haired pocket mice)	X			X	
Perognathus (silky pocket mice)	X		X		X
Family Muridae (mice, rats, voles)	X	X	X	X	X
Subfamily Arvicolinae (voles and lemmings)	X	X	X	X	X
Clethrionomys (red-backed voles)		X			
Microtus (meadow voles)	X	X	X	X	X
Ondatra (muskrats)		X		X	
Synaptomys (bog lemmings)		X			
Subfamily Cricetinae (hamsters)			X		
Subfamily Murinae (Old World rats and mice)	X	X		X	X
Mus (Old World mice)	X	X		X	X
Rattus (Old World rats)	X	X		X	
Subfamily Sigmodontinae (New World rats and mice)	X	X	X	X	X
Neotoma (packrats and woodrats)	X		X	X	X
Onychomys (grasshopper mice)		X	X		
Peromyscus (deer mice and white-footed mice)	X	X	X	X	X
Reithrodontomys (harvest mice)	X	X	X		X
Sigmodon (cotton rats)	X				
Family Sciuridae (squirrels)	X		X	X	X
Subfamily Pteromyinae (flying squirrels)	X				
Glaucomys (American flying squirrels)	X				
Subfamily Sciurinae (tree squirrels, ground squirrels, marmots, chipmunks)	X		X	X	X
Ammospermophilus (ground squirrels)	X		X	X	
Cynomys (prairie dogs)	X			X	
Marmota (marmots, woodchucks)	X	X		X	
Sciurus (tree squirrels)	X	X		X	
Spermophilus (ground squirrels and rock squirrels)	X		X	X	X
Tamias (chipmunks)	X			X	
Tamiasciurus (red squirrels)	X	X		X	X

[1]Source: University of Michigan 2004
[2]Source: California EPA 2003
[3]Source: U.S. EPA 1993

Table 3. Norway rat (*Rattus norvegicus*) and house mouse (*Mus musculus*) in diets of coyote, red fox, red-tailed hawk, and great horned owl.

Species	Location	Landscape	Time	Sample	Endpoint	% of diet				Reference
						R norvegicus	*M. musculus*	All rodents	*Rattus* + *Mus* (% of rodents)	
Coyote	IA	crops, pasture, woodlands	winter	stomach	volume	0	0.1	12.3	0.8	Andrews and Boggess 1978
	IA		spring-summer	scat	volume	0.7	0	24.6	2.8	Mathwig 1973
Red fox	MD		fall-winter	stomach	biomass	2.2	0	17.6	12.5	Hockman and Chapman 1983
	NE			stomach	volume	2.5	1.3	21.4	17.8	Powell and Case 1982
Red-tailed hawk	NJ,NY,CT	Forest		remains, pellets	number	3.2	1.2	53.1	8.3	Bosakowski and Smith 1992
Great horned owl	WA	agriculture, shrub-steppe	Oct-Jun	pellet	biomass	0	0.2	65.0	0.3	Knight and Jackman 198417
	ID		nesting season	pellet	biomass	0	0.7	41.5	1.7	Marti and Kochert 1996

Note: All other studies with these species (Appendix A) reported neither *R. norvegicus* nor *M. musculus* in diet. Neither rodent species was reported from any studies with kit fox.

Table 5. Estimated Field Metabolic Rate (FMR), and estimated and measured Food Ingestion Rate (FIR), for coyote, red fox, kit fox, red-tailed hawk, and great horned owl.

	FMR (kJ/d)		FIR (kg/kg/d)		
Species	Mean[1]	SD[2]	Mean[1]	SD[2]	Measured[3]
Coyote	7168	3170	0.136	0.038	0.052 – 0.131
Red fox	3299	1397	0.154	0.040	0.069 – 0.14
Kit fox	1802	473	0.166	0.040	0.029 – 0.18
Red-tailed hawk	462	172	0.084	0.031	0.055 – 0.112
Great horned owl	686	271	0.108	0.040	0.039 – 0.094

[1]Mean of 1,000 allometric estimates generated by Monte Carlo analysis
[2]Standard deviation of 1,000 estimates generated by Monte Carlo analysis
[3]Range of reported values (Table 6)

Table 6. Reported values for Food Ingestion Rate (FIR) of coyote, red fox, kit fox, red-tailed hawk, and great horned owl.

Species	FIR (kg/kg/d)	Reference	Notes
Coyote	0.052 - 0.131	Huegel and Rongstad 1985	field, deer and snowshoe hare diet, winter
Red Fox	0.075	Sargeant 1978	captive pair before whelping
	0.14	Sargeant 1978	captive pair after whelping
	0.069	Sargeant 1978	captive pair nonbreeding
Kit Fox	0.059	Golightly and Ohmart 1984	lab, desert kangaroo rat diet, summer; assume body wt = 1936 g
	0.052	Golightly and Ohmart 1984	lab, desert kangaroo rat diet, winter, assume body wt = 1936 g
	0.056 - 0.18	Egoscue 1962	lab, male, assume body wt = 1936 g
	0.029 - 0.15	Egoscue 1962	lab, female, assume body wt = 1936 g
Red-tailed Hawk	0.112	Craighead and Craighead 1956	captive female, winter, fed raw beef plus natural prey
	0.102	Craighead and Craighead 1956	captive male, winter, fed raw beef plus natural prey
	0.086	Craighead and Craighead 1956	captive male, summer, fed raw beef plus natural prey
	0.055	Duke et al. 1976	captive, fed mice
Great Horned Owl	0.039	Duke et al. 1973	lab, mouse or turkey diet, reported on dry weight basis, assume moisture content = 68%
	0.094	Tabaka et al. 1996	lab, chick diet, assume body wt = 1229 g
	0.093	Tabaka et al. 1996	lab, hamster diet, assume body wt = 1229 g
	0.047	Marti 1973	lab, mouse diet, reported on dry weight basis, assume moisture content = 68%, sedentary individual, all seasons
	0.067 - 0.069	Craighead and Craighead 1969	lab, spring, assume body wt = 1229 g

Data extracted from California EPA 2003 and U.S. EPA 1993

Table 7. Summary of daily dose model runs with brodifacoum.

Species	Model Run	PD[a]	PT[b]	DD Mean[c]	DD CV[d]
Coyote	DD008	0.1985	0.01	0.00056	15.165
Coyote	DD001	0.1985	0.025	0.00122	10.631
Coyote	DD002	0.1985	0.05	0.00238	7.559
Coyote	DD003	0.1985	0.075	0.00335	6.162
Coyote	DD004	0.1985	0.10	0.00617	5.498
Coyote	DD005	0.1985	0.15	0.00803	4.305
Coyote	DD006[e]	0.1985	0.025	0.00124	11.076
Coyote	DD007[f]	0.1985	0.025	0.00117	10.137
Red fox	RF_DD002	0.1988	0.01	0.00055	15.295
Kit fox	KF_DD002	0.6329	0.01	0.00158	15.317
Red-tailed hawk	RTH_DD002	0.4925	0.01	0.00096	14.316
Great horned owl	GHO_DD002	0.6994	0.01	0.00175	14.125
Red fox	RF_DD001	0.1988	0.025	0.00125	9.779
Kit fox	KF_DD001	0.6329	0.025	0.00441	9.222
Red-tailed hawk	RTH_DD001	0.4925	0.025	0.00194	9.334
Great horned owl	GHO_DD001	0.6994	0.025	0.00345	9.356

[a] Fraction of rodents in diet. Each value shown is the mean of a beta distribution fitted to field data. The entire beta distribution was used as input to the daily dose model.
[b] Fraction of rodents in diet that have been exposed to brodifacoum (input assumption).
[c] Daily dose mean (mg/kg/d). Each value shown is the mean of a beta distribution fitted to the daily dose means for 100 individuals. For each individual, the daily dose mean is the mean of 1,000 simulated daily doses.
[d] Daily dose coefficient of variation. Each value shown is the mean of a gamma distribution fitted to the daily dose CVs for 100 individuals. For each individual, the daily dose CV is the CV of 1,000 simulated daily doses.
[e] Daily PD standard deviation = 10 (default value = 5)
[f] Daily PD standard deviation = 3 (default value = 5)

Table 8. Summary of cumulative dose model runs with brodifacoum and coyote: sensitivity to halflife.

	90-d max (mg/kg); PT = 0.01[a]			90-d max (mg/kg); PT = 0.025[a]			90-d max (mg/kg); PT = 0.10[a]		
Halflife (d)[b]	Model Run	Mean[c]	90%ile[d]	Model Run	Mean[c]	90%ile[d]	Model Run	Mean[c]	90%ile[d]
200	CD008-002	0.0509	0.1396	CD001-004	0.0936	0.2076	CD004-001	0.4627	1.0232
100	CD008-003	0.0397	0.1168	CD001-003	0.0781	0.1866	CD004-002	0.4136	0.8998
50	CD008-001	0.0409	0.1188	CD001-002	0.0850	0.2217	CD004-003	0.2543	0.5223
20	CD008-004	0.0301	0.0799	CD001-001	0.0657	0.1567	CD004-004	0.2730	0.6253
10	CD008-005	0.0269	0.0666	CD001-005	0.0554	0.1325	CD004-005	0.2050	0.4258
5	CD008-006	0.0254	0.0646	CD001-006	0.0499	0.1220	CD004-006	0.1535	0.3098
2	CD008-007	0.0269	0.0691	CD001-007	0.0450	0.1025	CD004-007	0.1555	0.3311

[a] Assumed fraction of rodents in diet exposed to brodifacoum
[b] Assumed first-order depuration halflife
[c] Mean of means for 100 individuals
[d] 90th percentile (10% exceedence value) of means for 100 individuals

Table 9. Summary of cumulative dose model runs with brodifacoum and coyote: sensitivity to PT (percent treated rodents in diet).

Model Run	PT[a]	Halflife (d)[b]	90-d Max (mg/kg)	
			Mean[c]	90%ile[d]
CD008-001	0.01	50	0.0409	0.1188
CD001-002	0.025	50	0.0850	0.2217
CD002-001	0.050	50	0.1527	0.3243
CD003-001	0.075	50	0.2146	0.5078
CD004-003	0.10	50	0.2543	0.5223
CD005-001	0.15	50	0.4540	1.0056

[a] Assumed fraction of rodents in diet exposed to brodifacoum
[b] Assumed first-order depuration halflife
[c] Mean of means for 100 individuals
[d] 90th percentile (10% exceedence value) of means for 100 individuals

Table 10. Summary of cumulative dose model runs with brodifacoum and coyote: effect of run duration on cumulative dose estimate.

Model Run	PT[a]	Halflife (d)[b]	Duration of Run (d)	Maximum dose (mg/kg)	
				Mean[c]	90%ile[d]
CD001-006	0.025	5	90	0.0499	0.1220
CD001-011	0.025	5	180	0.0841	0.2322
CD001-010	0.025	5	360	0.1031	0.2349
CD001-002	0.025	50	90	0.0850	0.2217
CD001-009	0.025	50	180	0.1251	0.3321
CD001-008	0.025	50	360	0.1782	0.4071
CD001-004	0.025	200	90	0.0936	0.2076
CD001-013	0.025	200	180	0.1542	0.3481
CD001-012	0.025	200	360	0.3094	0.6644

Table 11. Summary of cumulative dose model runs with brodifacoum and five species of predators.

Species	Model Run	PT[a]	Halflife (d)[b]	90-d Max (mg/kg)	
				Mean[c]	90%ile[d]
Coyote	CD008-001	0.01	50	0.0409	0.1188
Red Fox	RF_CD002-001	0.01	50	0.0387	0.0764
Kit Fox	KF_CD002-001	0.01	50	0.1041	0.2012
Red-tailed Hawk	RTH_CD002-001	0.01	50	0.0649	0.1409
Great Horned Owl	GHO_CD002-001	0.01	50	0.1166	0.2590
Coyote	CD001-002	0.025	50	0.0850	0.2217
Red Fox	RF_CD001-001	0.025	50	0.0784	0.1462
Kit Fox	KF_CD001-001	0.025	50	0.2948	0.5325
Red-tailed Hawk	RTH_CD001-001	0.025	50	0.1199	0.2254
Great Horned Owl	GHO_CD001-001	0.025	50	0.2018	0.4218

[a] Assumed fraction of rodents in diet exposed to brodifacoum
[b] Assumed first-order depuration halflife
[c] Mean of means for 100 individuals
[d] 90th percentile (10% exceedence value) of means for 100 individuals

Table 12. Mammalian effects model parameters.

Species	Parameter	2.5%	Median	97.5%
Dog	α	-1.94	-1.20	-0.57
	β	0.61	1.18	1.85
	LD_{50}	1.79	2.76	5.04
Feral pigs	α	0.12	1.50	3.28
	β	0.89	2.22	4.00
	LD_{50}	0.26	0.50	0.93
Guinea pig	α	-4.60	-2.40	-0.86
	β	1.14	2.35	4.06
	LD_{50}	1.64	2.81	4.81
Mouse	α	1.70	4.45	8.63
	β	2.06	4.16	7.83
	LD_{50}	0.22	0.35	0.53
Rabbit	α	2.24	3.84	5.83
	β	1.49	2.64	4.02
	LD_{50}	0.16	0.23	0.31
Rat	α	2.90	4.43	6.73
	β	3.84	5.73	8.63
	LD_{50}	0.42	0.46	0.51
Sheep	α	-6.76	-3.73	-1.57
	β	0.42	1.57	3.03
	LD_{50}	6.27	10.75	73.91
Wallaby	α	-1.14	-0.33	0.49
	β	0.57	1.55	2.79
	LD_{50}	0.76	1.24	3.72
Integrated Model	α	-2.13	0.85	3.87
	β	1.20	2.71	4.44
	LD_{50}	0.18	0.73	2.34

Table 13. Avian effects model parameters.

Species	Parameter	2.5%	Median	97.5%
California quail	α	-6.12	-3.06	-1.06
	β	1.29	2.86	5.33
	LD_{50}	1.71	2.93	5.44
Harrier hawk	α	-7.41	-3.67	-0.69
	β	0.38	1.62	3.20
	LD_{50}	3.18	9.56	30.48
Chicken (1975)	α	-5.68	-3.01	-0.73
	β	0.32	0.98	1.77
	LD_{50}	6.64	21.63	45.61
Chicken (1977)	α	-5.65	-3.06	-0.88
	β	0.99	1.93	3.16
	LD_{50}	2.25	4.84	7.41
Japanese quail	α	-9.77	-7.38	-4.19
	β	1.73	3.02	4.03
	LD_{50}	9.29	11.50	14.20
Mallard	α	1.74	2.91	4.68
	β	1.69	2.50	3.70
	LD_{50}	0.22	0.31	0.43
Pheasant (1986)	α	-0.80	0.02	0.96
	β	0.12	0.37	0.80
	LD_{50}	0.20	0.94	214.6
Pheasant (1985)	α	-8.45	-3.90	0.04
	β	0.56	1.95	3.60
	LD_{50}	0.94	7.41	14.4
Pukeko	α	-1.74	-0.35	0.94
	β	0.91	2.28	4.22
	LD_{50}	0.54	1.16	1.97
Integrated Model	α	-5.23	-2.38	0.14
	β	1.05	1.96	3.13
	LD_{50}	0.93	3.37	18.55

Table 14. Summary of brodifacoum risk to five predator species: mortality rate (%) at 10%, 50%, and 90% exceedence probabilities.

Model Run[a]	Assumptions			Exceedence Probability		
Coyote	PT[b]	Halflife	Sensitivity	10%	50%	90%
CD008-001	0.01	50 d	high	7[c]	2	≤1
CD008-001	0.01	50 d	median	2	≤1	≤1
CD008-001	0.01	50 d	low	≤1	≤1	≤1
CD001-002	0.025	50 d	high	18	4	≤1
CD001-002	0.025	50 d	median	4	≤1	≤1
CD001-002	0.025	50 d	low	2	≤1	≤1
Red Fox	PT	Halflife	Sensitivity	10%	50%	90%
RF_CD002-001	0.01	50 d	high	5	≤1	≤1
RF_CD002-001	0.01	50 d	median	≤1	≤1	≤1
RF_CD002-001	0.01	50 d	low	≤1	≤1	≤1
RF_CD001-001	0.025	50 d	high	16	2	≤1
RF_CD001-001	0.025	50 d	median	3	≤1	≤1
RF_CD001-001	0.025	50 d	low	≤1	≤1	≤1
Kit Fox	PT	Halflife	Sensitivity	10%	50%	90%
KF_CD002-001	0.01	50 d	high	23	4	≤1
KF_CD002-001	0.01	50 d	median	5	≤1	≤1
KF_CD002-001	0.01	50 d	low	2	≤1	≤1
KF_CD001-001	0.025	50 d	high	67	25	5
KF_CD001-001	0.025	50 d	median	28	6	≤1
KF_CD001-001	0.025	50 d	low	9	2	≤1
Red-tailed Hawk	PT	Halflife	Sensitivity	10%	50%	90%
RTH_CD002-001	0.01	50 d	high	11	2	≤1
RTH_CD002-001	0.01	50 d	median	2	≤1	≤1
RTH_CD002-001	0.01	50 d	low	≤1	≤1	≤1
RTH_CD001-001	0.025	50 d	high	32	5	≤1
RTH_CD001-001	0.025	50 d	median	6	≤1	≤1
RTH_CD001-001	0.025	50 d	low	2	≤1	≤1
Great Horned Owl	PT	Halflife	Sensitivity	10%	50%	90%
GHO_CD002-001	0.01	50 d	high	25	6	2
GHO_CD002-001	0.01	50 d	median	7	2	≤1
GHO_CD002-001	0.01	50 d	low	2	≤1	≤1
GHO_CD001-001	0.025	50 d	high	52	13	3
GHO_CD001-001	0.025	50 d	median	15	3	≤1
GHO_CD001-001	0.025	50 d	low	5	≤1	≤1

[a] See Table 11 for details.
[b] PT = proportion of rodents in the diet that have been exposed to brodifacoum.
[c] Interpretation: there is a 10% probability that the coyote mortality rate exceeds 7% under the assumptions of this model run.

Table 15. Summary of brodifacoum risk to coyote under different assumptions about halflife: mortality rate (%) at 10%, 50%, and 90% exceedence probabilities.

Model Run[a]	Assumptions			Exceedence Probability		
Coyote	PT[b]	Halflife	Sensitivity	10%	50%	90%
CD001-007	0.025	2 d	high	7[c]	2	≤1
CD001-005	0.025	10 d	high	10	2	≤1
CD001-001	0.025	20 d	high	13	3	≤1
CD001-002	0.025	50 d	high	18	4	≤1
CD001-004	0.025	200 d	high	21	5	≤1

[a] See Table 8 for details.
[b] PT = proportion of rodents in the diet that have been exposed to brodifacoum.
[c] Interpretation: there is a 10% probability that the coyote mortality rate exceeds 7% under the assumptions of this model run.

Table 16. Summary of brodifacoum risk to coyote under different assumptions about PT: mortality rate (%) at 10%, 50%, and 90% exceedence probabilities.

Model Run[a]	Assumptions			Exceedence Probability		
Coyote	PT[b]	Halflife	Sensitivity	10%	50%	90%
CD008-001	0.01	50 d	high	7[c]	2	≤1
CD001-002	0.025	50 d	high	18	4	≤1
CD002-001	0.05	50 d	high	42	8	2
CD004-003	0.10	50 d	high	57	20	5

[a] See Table 9 for details.
[b] PT = proportion of rodents in the diet that have been exposed to brodifacoum.
[c] Interpretation: there is a 10% probability that the coyote mortality rate exceeds 7% under the assumptions of this model run.

Figures

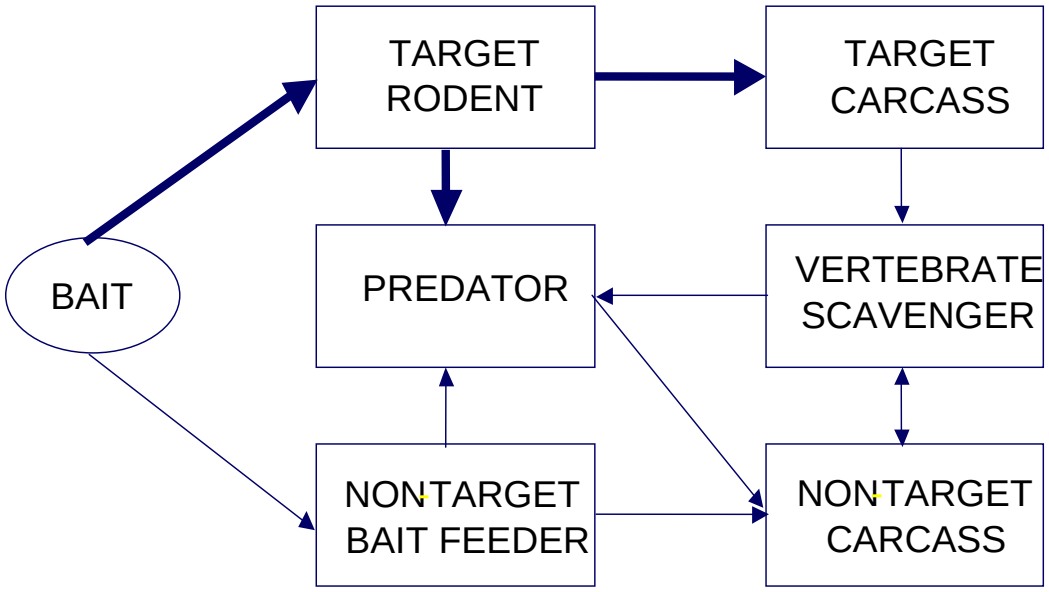


Figure 1. Schematic representation of the flow of brodifacoum through vertebrates in a terrestrial ecosystem.

Bold arrows represent major routes of brodifacoum movement.

Provided by Spencer Mortensen, Syngenta Crop Protection.

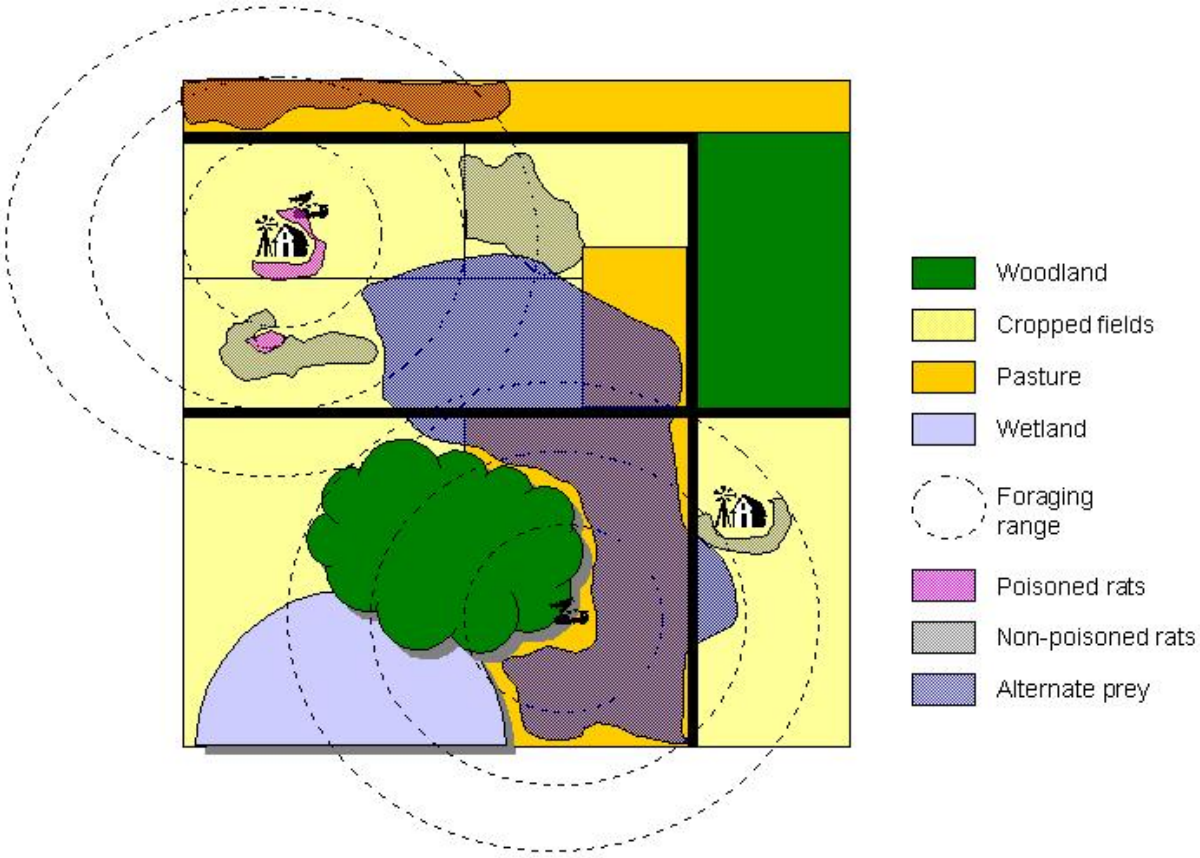


Figure 2. Conceptual model of non-target exposure: example of rural landscape showing secondary exposure of owls to brodifacoum used to control commensal rodents in and around farm buildings.

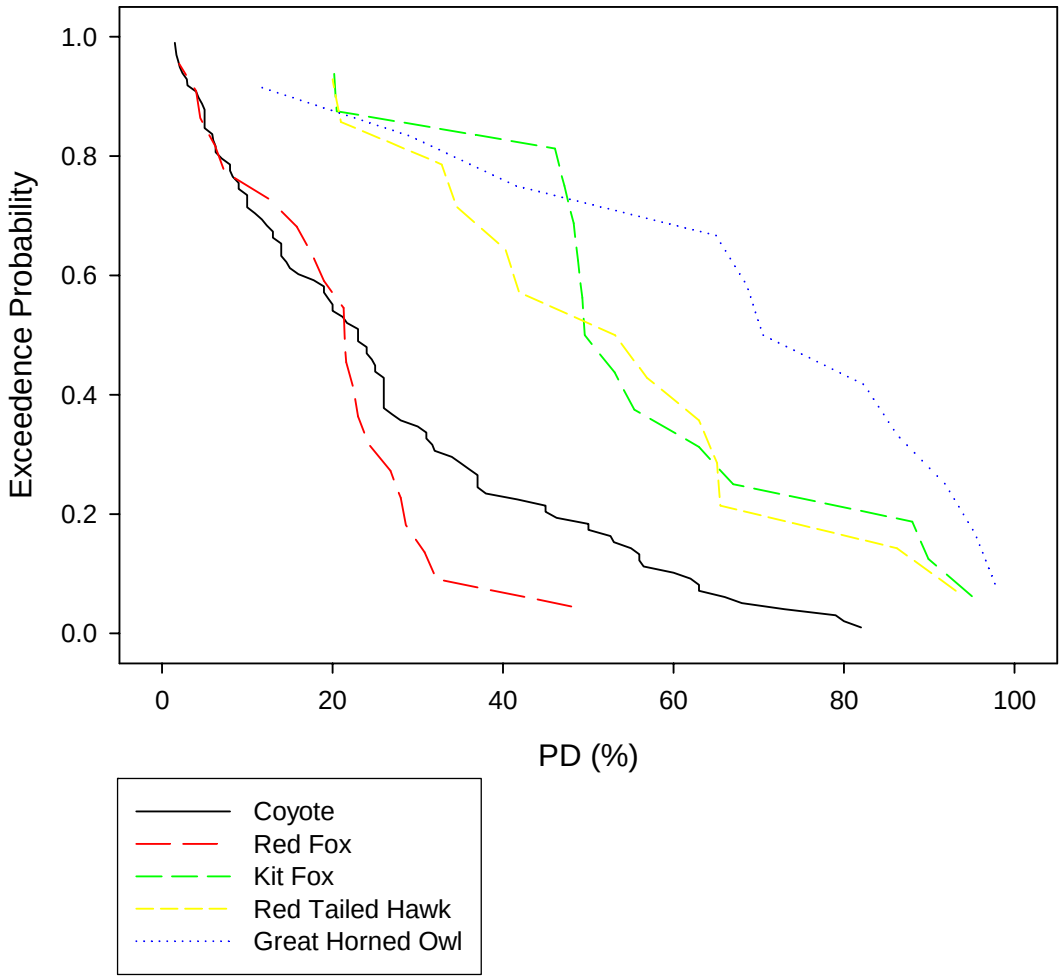


Figure 3. Distributions of field data on PD (percentage rodents in diet) for coyote, red fox, kit fox, red-tailed hawk, and great horned owl.

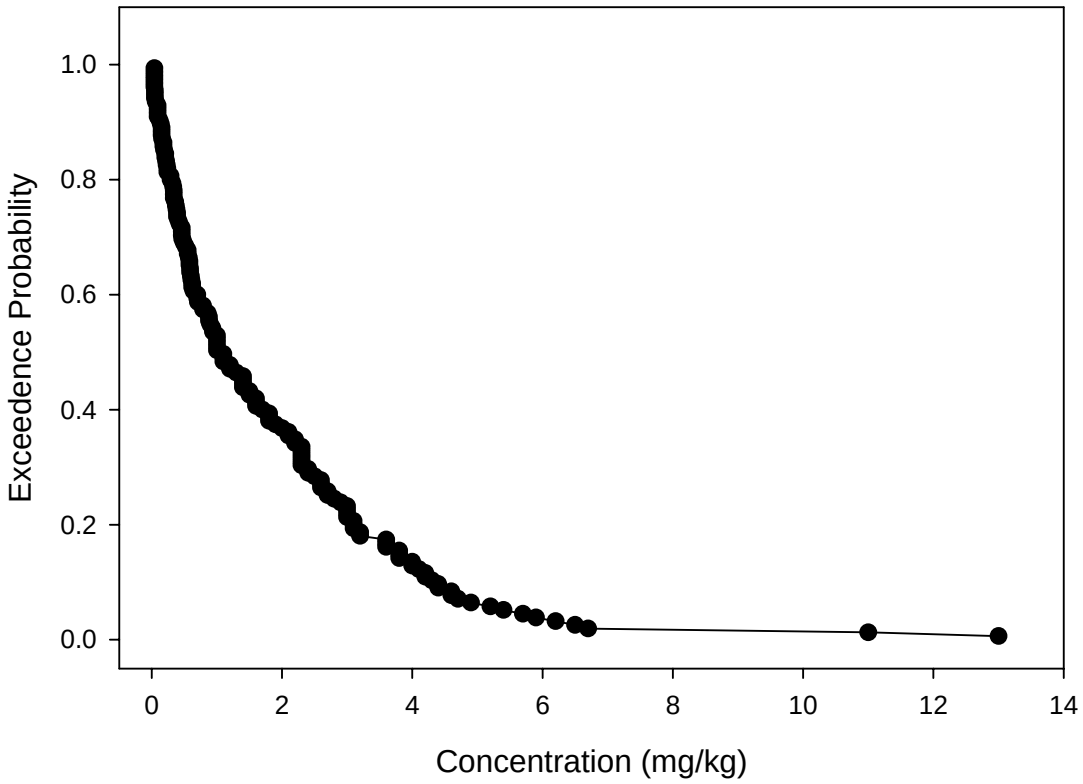
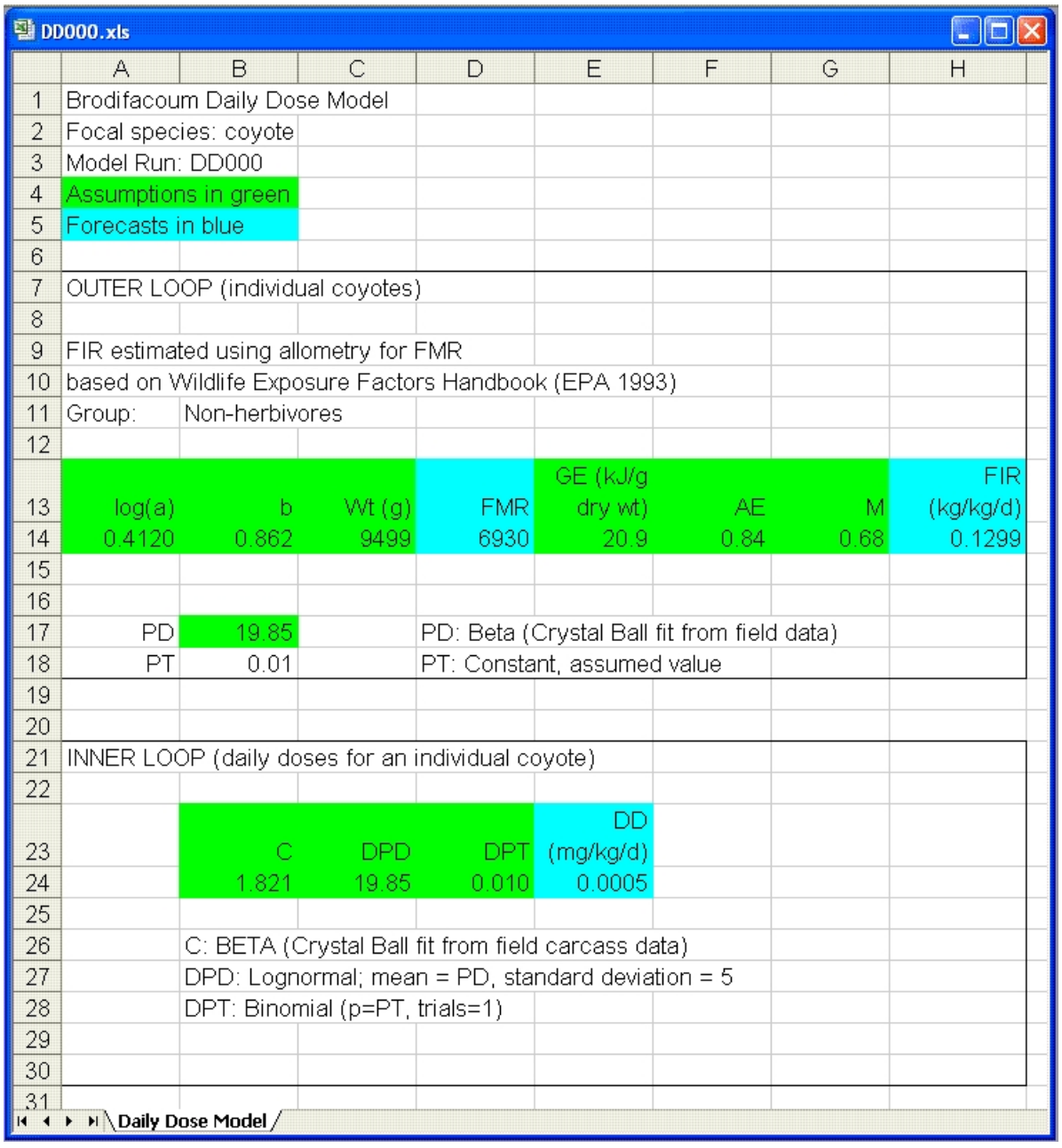


Figure 4. Distribution of brodifacoum concentrations in rodent carcasses collected in field trials.

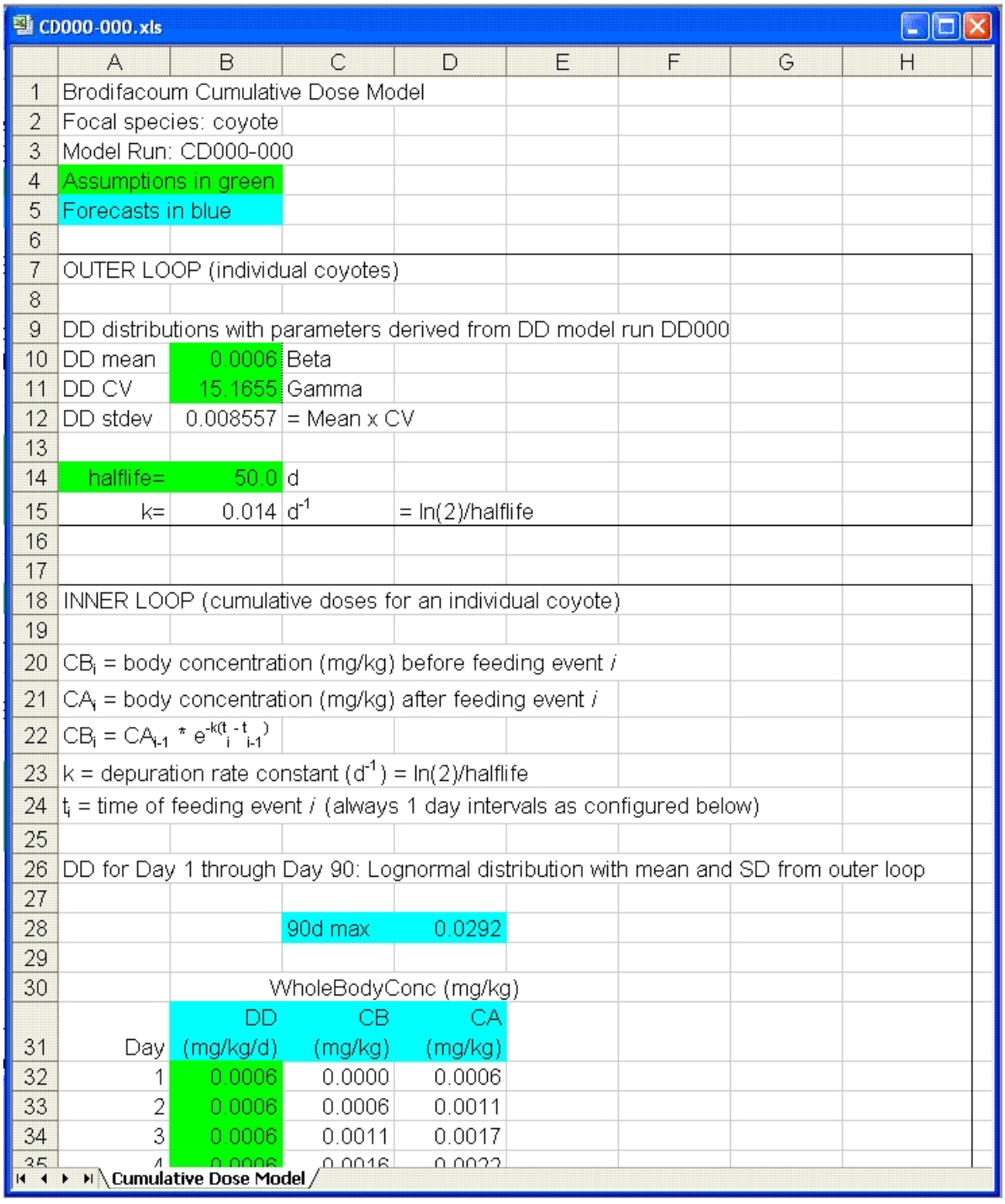


DD000.xls

	A	B	C	D	E	F	G	H
1	Brodifacoum Daily Dose Model							
2	Focal species: coyote							
3	Model Run: DD000							
4	Assumptions in green							
5	Forecasts in blue							
6								
7	OUTER LOOP (individual coyotes)							
8								
9	FIR estimated using allometry for FMR							
10	based on Wildlife Exposure Factors Handbook (EPA 1993)							
11	Group:	Non-herbivores						
12								
13	log(a)	b	Wt (g)	FMR	GE (kJ/g dry wt)	AE	M	FIR (kg/kg/d)
14	0.4120	0.862	9499	6930	20.9	0.84	0.68	0.1299
15								
16								
17	PD	19.85		PD: Beta (Crystal Ball fit from field data)				
18	PT	0.01		PT: Constant, assumed value				
19								
20								
21	INNER LOOP (daily doses for an individual coyote)							
22								
23		C	DPD	DPT	DD (mg/kg/d)			
24		1.821	19.85	0.010	0.0005			
25								
26		C: BETA (Crystal Ball fit from field carcass data)						
27		DPD: Lognormal; mean = PD, standard deviation = 5						
28		DPT: Binomial (p=PT, trials=1)						
29								
30								
31								

Daily Dose Model

Figure 5. Implementation of the daily dose model in an Excel spreadsheet with Crystal Ball.



CD000-000.xls

	A	B	C	D	E	F	G	H
1	Brodifacoum Cumulative Dose Model							
2	Focal species: coyote							
3	Model Run: CD000-000							
4	Assumptions in green							
5	Forecasts in blue							
6								
7	OUTER LOOP (individual coyotes)							
8								
9	DD distributions with parameters derived from DD model run DD000							
10	DD mean	0.0006	Beta					
11	DD CV	15.1655	Gamma					
12	DD stdev	0.008557	= Mean x CV					
13								
14	halflife=	50.0	d					
15	k=	0.014	d^{-1}	= ln(2)/halflife				
16								
17								
18	INNER LOOP (cumulative doses for an individual coyote)							
19								
20	CB_i = body concentration (mg/kg) before feeding event *i*							
21	CA_i = body concentration (mg/kg) after feeding event *i*							
22	$CB_i = CA_{i-1} * e^{-k(t_i - t_{i-1})}$							
23	k = depuration rate constant (d^{-1}) = ln(2)/halflife							
24	t_i = time of feeding event *i* (always 1 day intervals as configured below)							
25								
26	DD for Day 1 through Day 90: Lognormal distribution with mean and SD from outer loop							
27								
28			90d max	0.0292				
29								
30			WholeBodyConc (mg/kg)					
31	Day	DD (mg/kg/d)	CB (mg/kg)	CA (mg/kg)				
32	1	0.0006	0.0000	0.0006				
33	2	0.0006	0.0006	0.0011				
34	3	0.0006	0.0011	0.0017				
35	4	0.0006	0.0016	0.0022				

Cumulative Dose Model

Figure 6. Implementation of the cumulative dose model in an Excel spreadsheet with Crystal Ball.

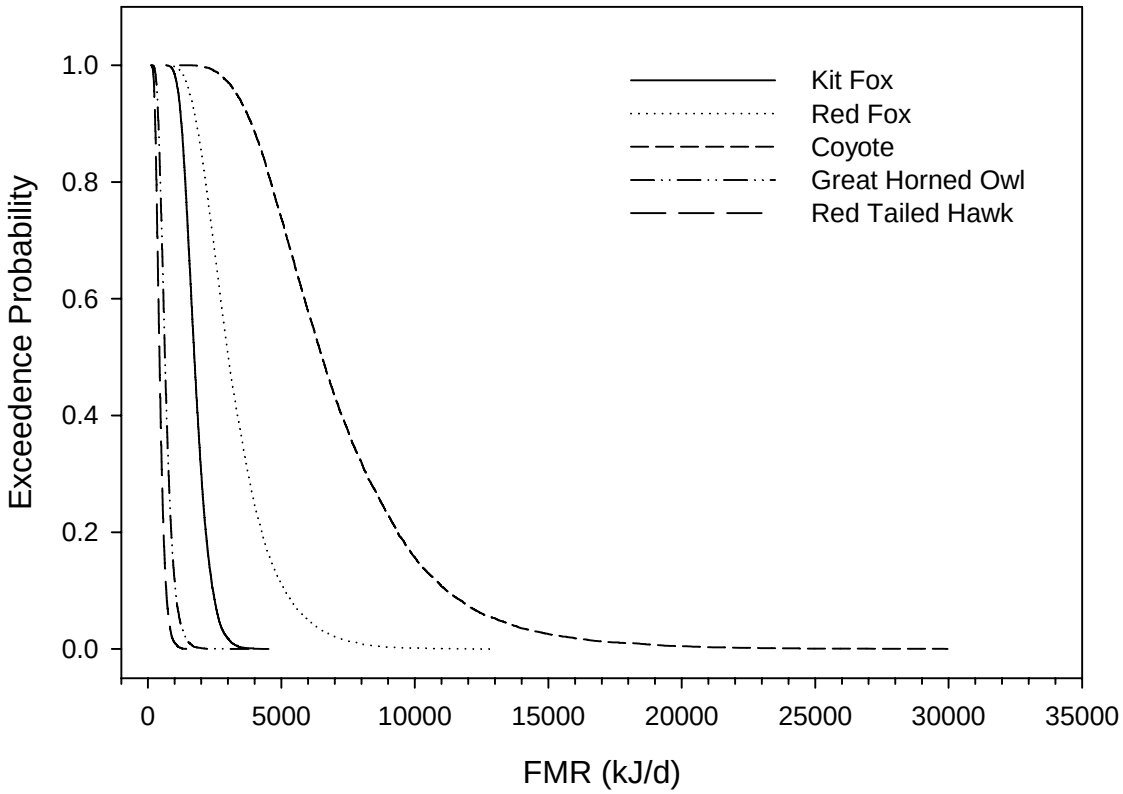


Figure 7. Distributions of predicted field metabolism rates (FMR) for coyote, red fox, kit fox, red-tailed hawk, and great horned owl, showing variability among individuals due to variability in body weight and uncertainty about allometric parameters

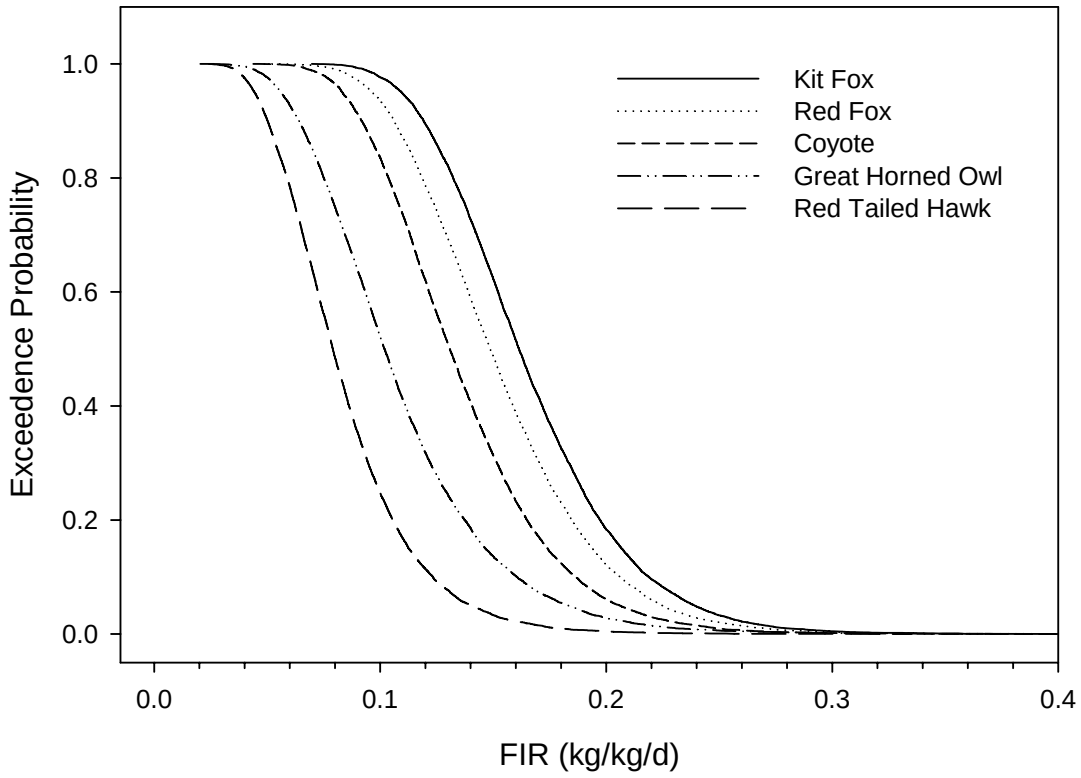


Figure 8. Distributions of predicted food ingestion rates (FIR) for coyote, red fox, kit fox, red-tailed hawk, and great horned owl.

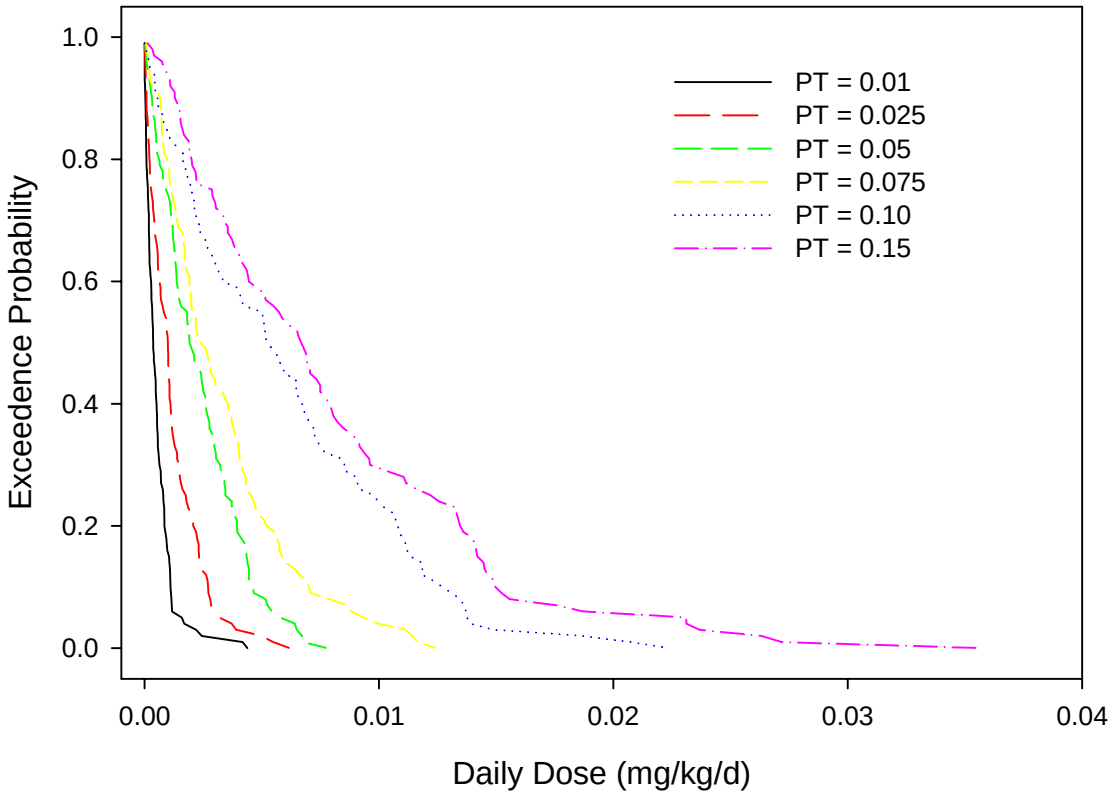


Figure 9. Reverse cumulative frequency distributions of brodifacoum daily dose estimations for coyote under different assumptions about the fraction of rodents in the diet that are exposed to brodifacoum (PT).

N = 100 for each distribution. Each point in the distribution is the mean of the daily dose distribution for one individual.

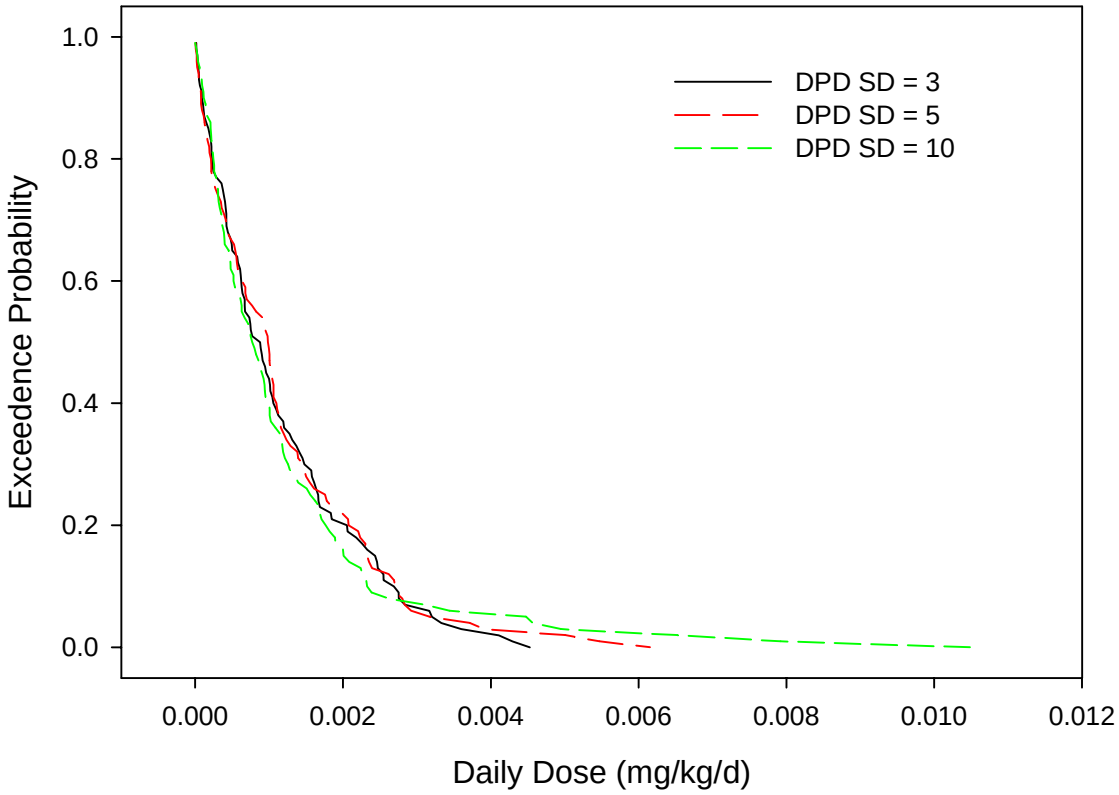


Figure 10. Reverse cumulative frequency distributions of daily mean dose of brodifacoum for coyote assuming PT = 0.025, with three different assumptions about the day-to-day variation in PD (represented in the model as the standard deviation of Daily PD).

N = 100 for each distribution. Each point in the distribution is the mean of the daily dose distribution for one individual.

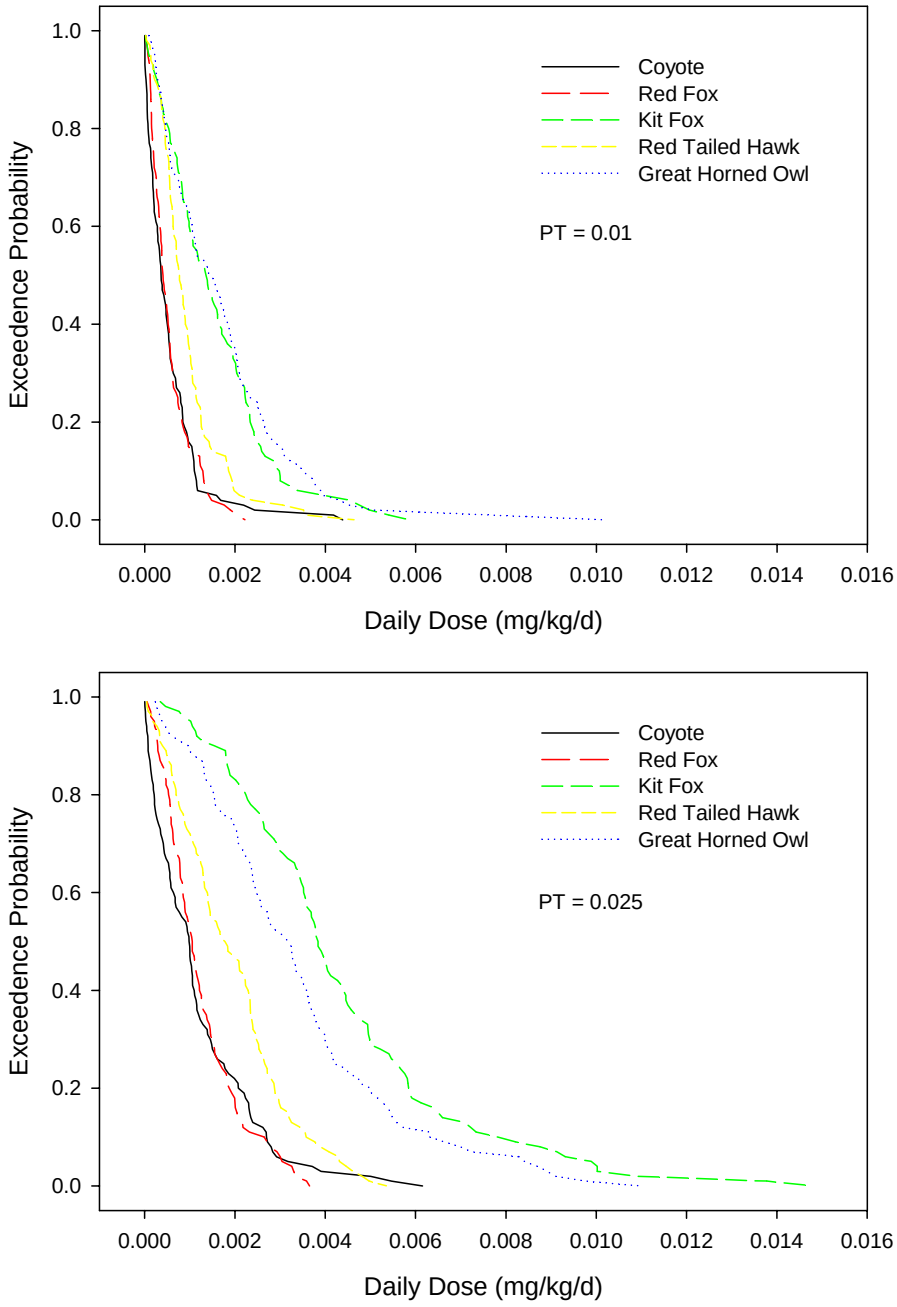


Figure 11. Reverse cumulative frequency distributions of mean daily dose of brodifacoum for five predator species.

N = 100 for each distribution. Each point in the distribution is the mean of the daily dose distribution for one individual.

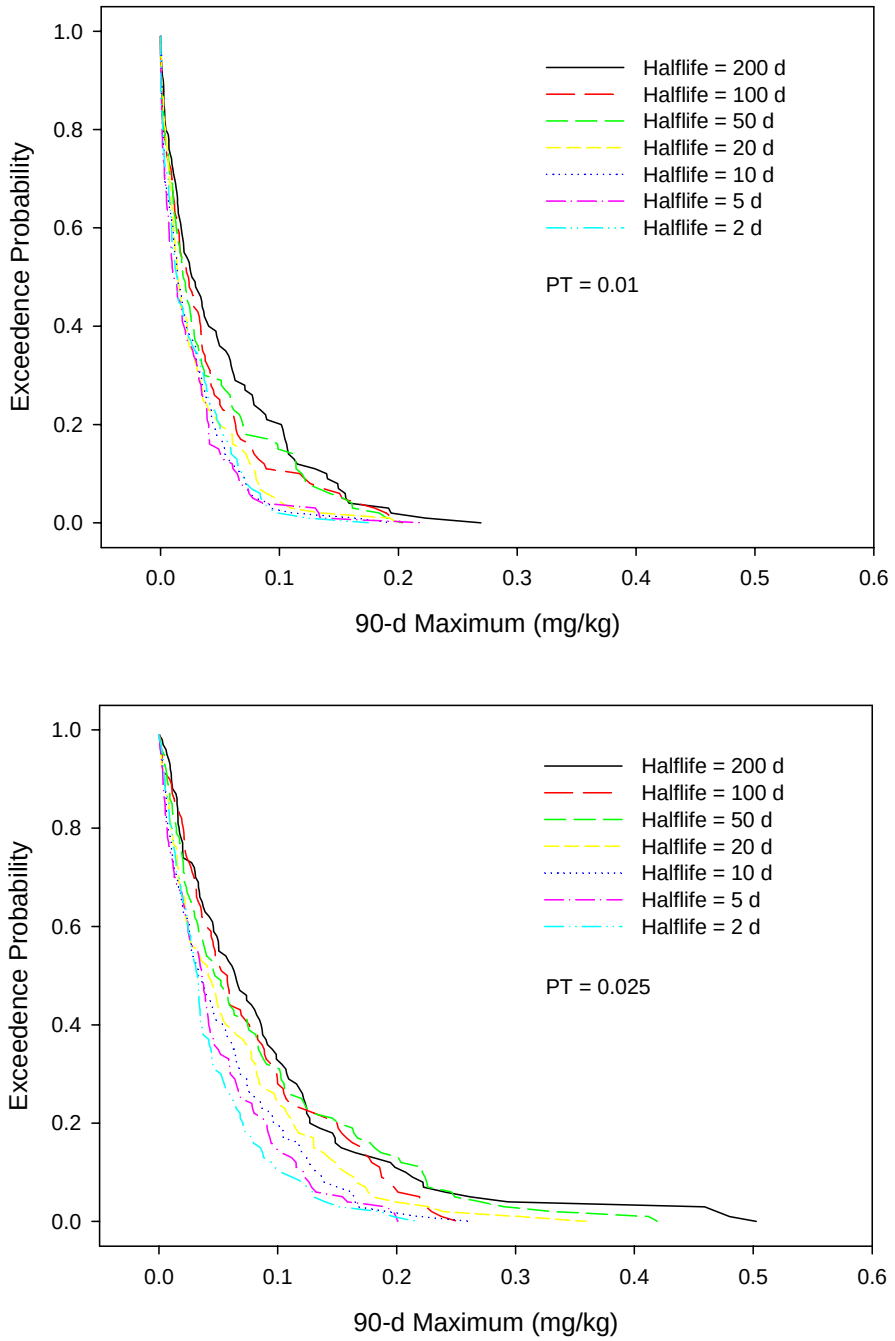


Figure 12. Reverse cumulative frequency distributions of estimated cumulative dose (90-day maximum concentrations) to coyote under different assumptions about the halflife of brodifacoum in the body.

N = 100 for each distribution. Each point in the distribution is the mean of the cumulative dose distribution for one individual.

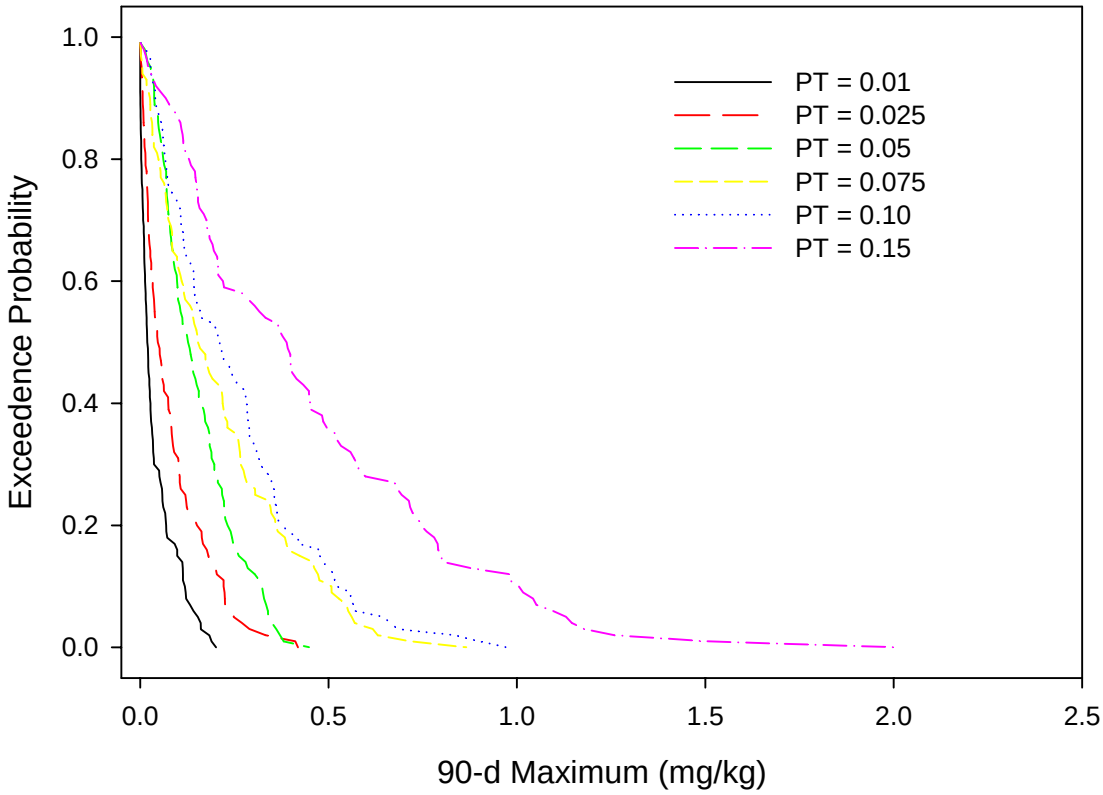


Figure 13. Reverse cumulative frequency distributions of estimated cumulative dose (90-day maximum concentrations) to coyote under different assumptions about the fraction of rodents in the diet that are exposed to brodifacoum (PT). Halflife = 50 d.

N = 100 for each distribution. Each point in the distribution is the mean of the cumulative dose distribution for one individual.

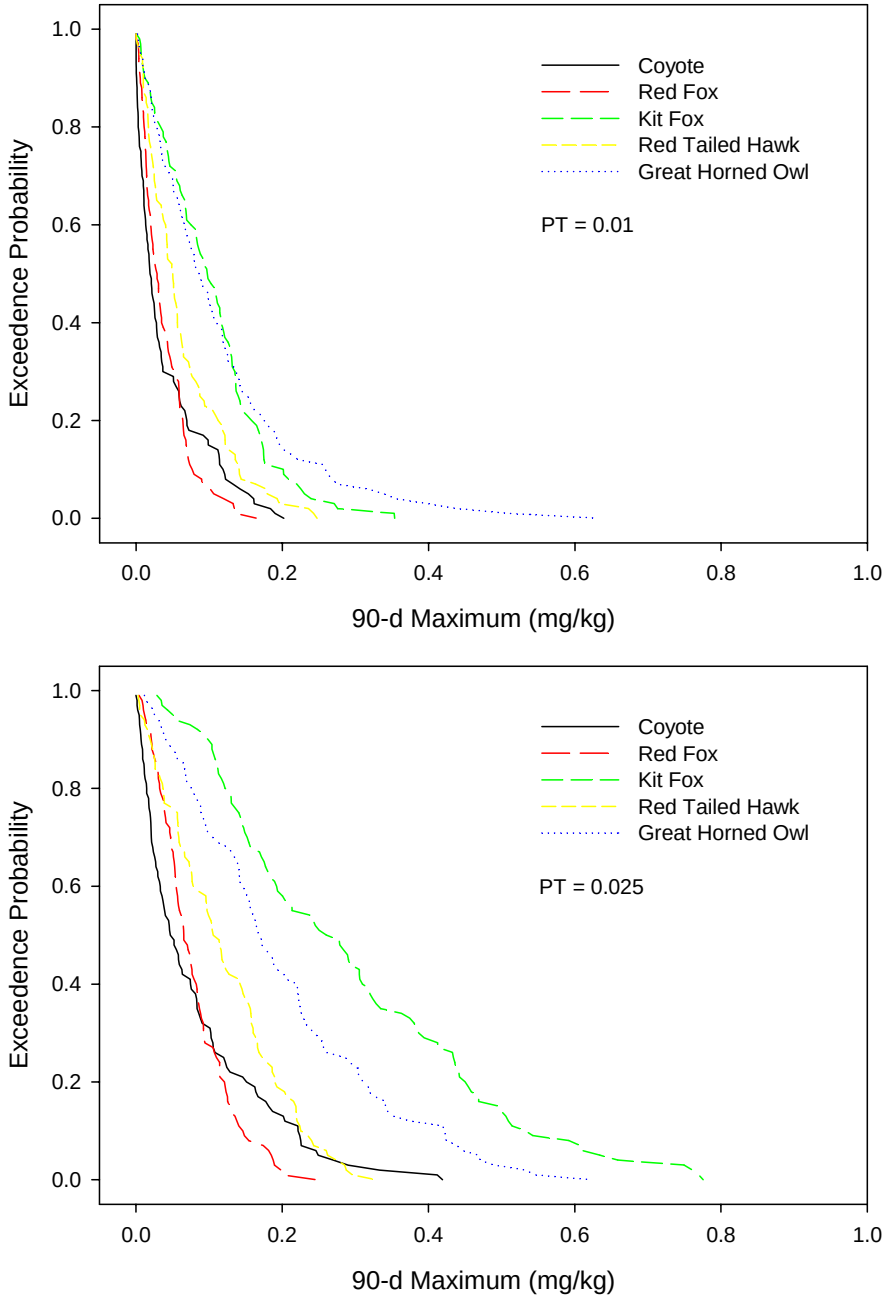


Figure 14. Reverse cumulative frequency distributions of estimated cumulative dose (90-day maximum concentrations) to five predator species.

N = 100 for each distribution. Each point in the distribution is the mean of the 90-d maximum cumulative dose distribution for one individual.

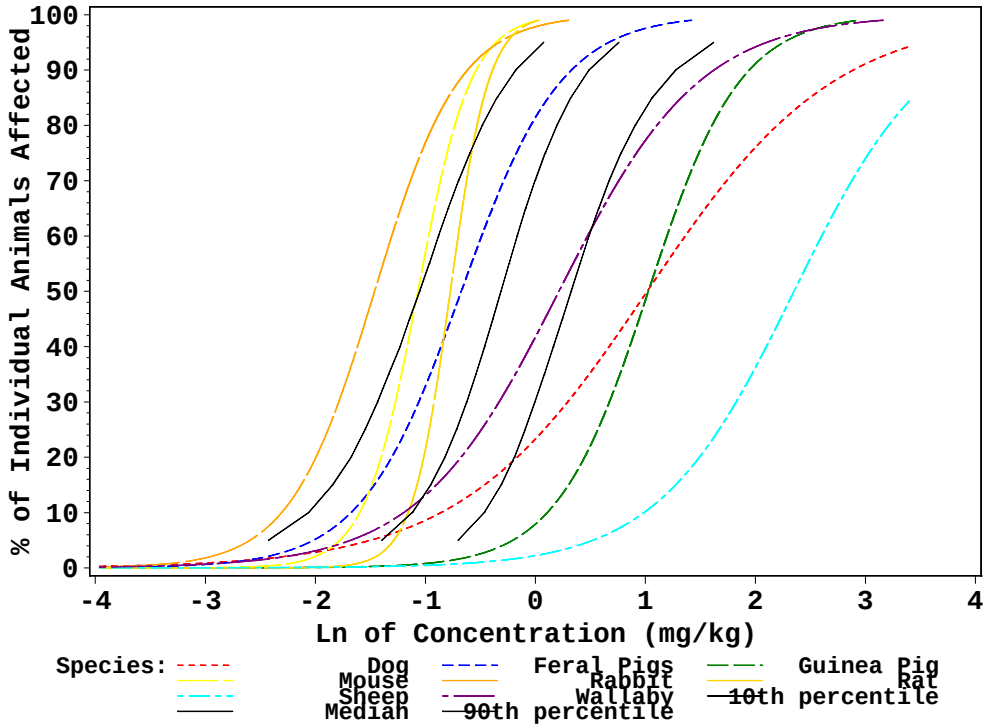


Figure 15. Dose-response models for mammals.

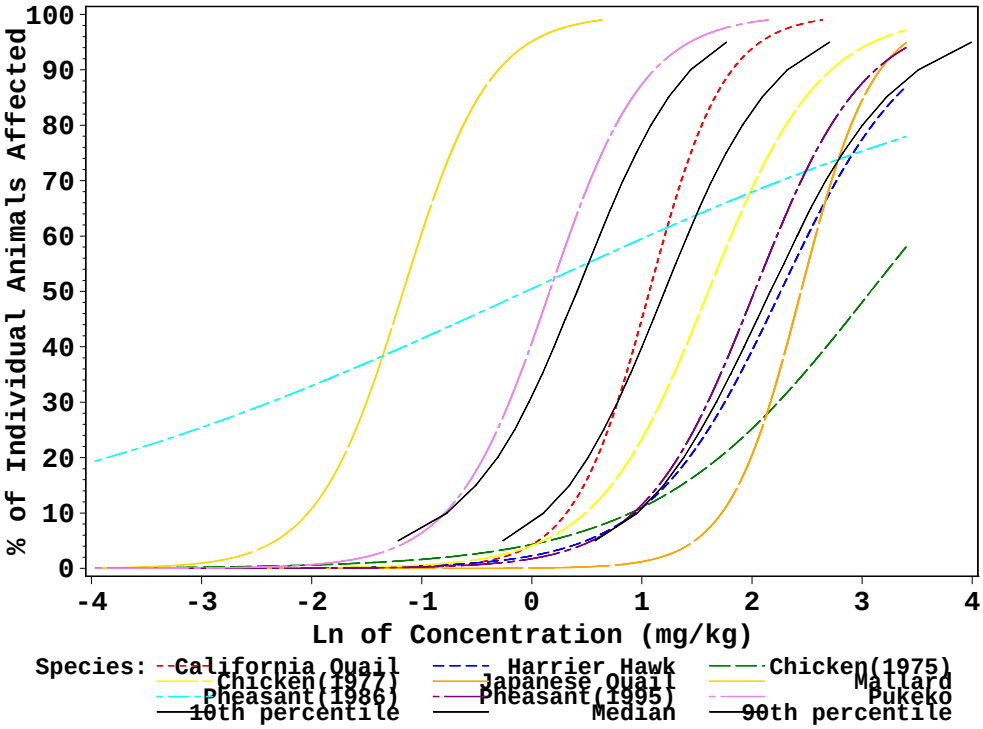


Figure 16. Dose-response models for birds.

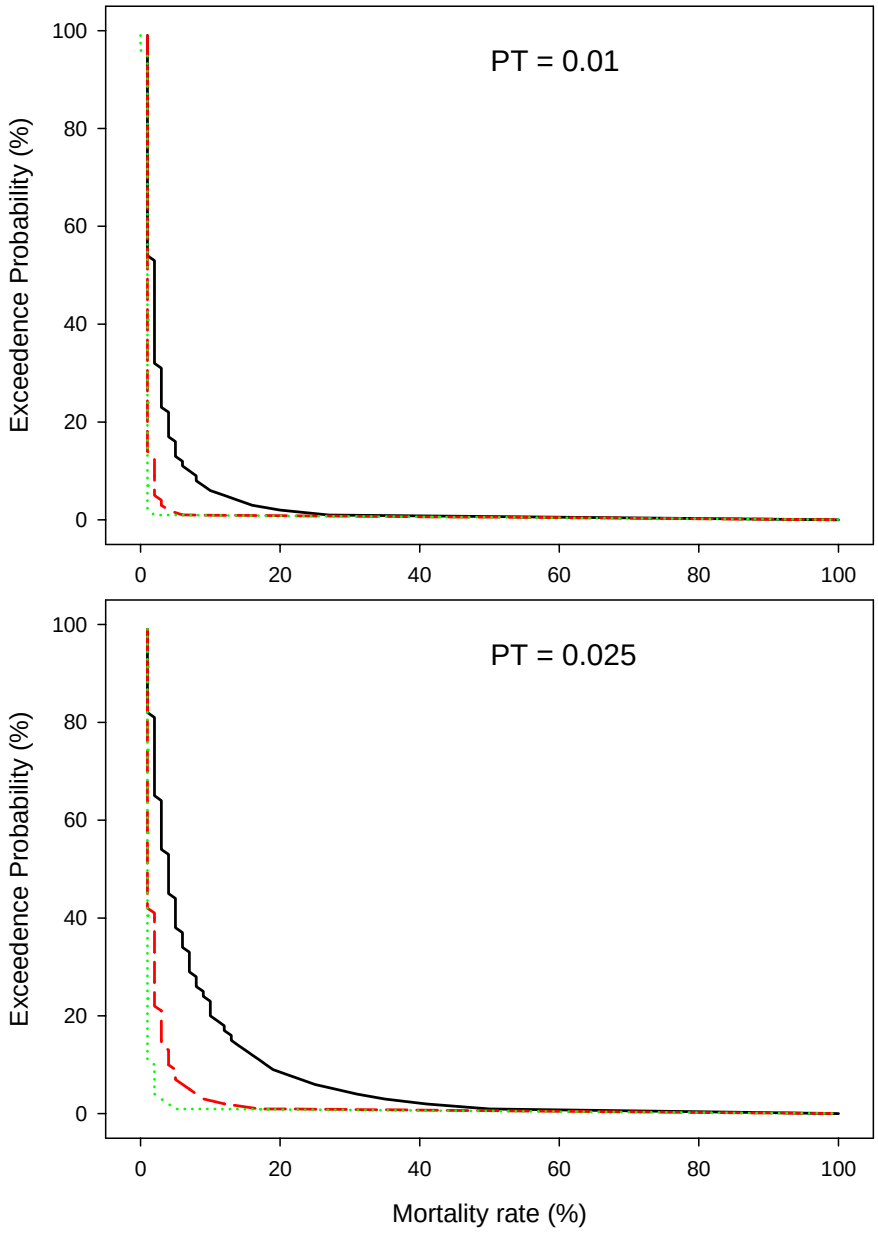


Figure 17. Risk curves for coyote.

Each plot shows lines representing assumptions of low sensitivity (dotted line), median sensitivity (dashed line), and high sensitivity (solid line).

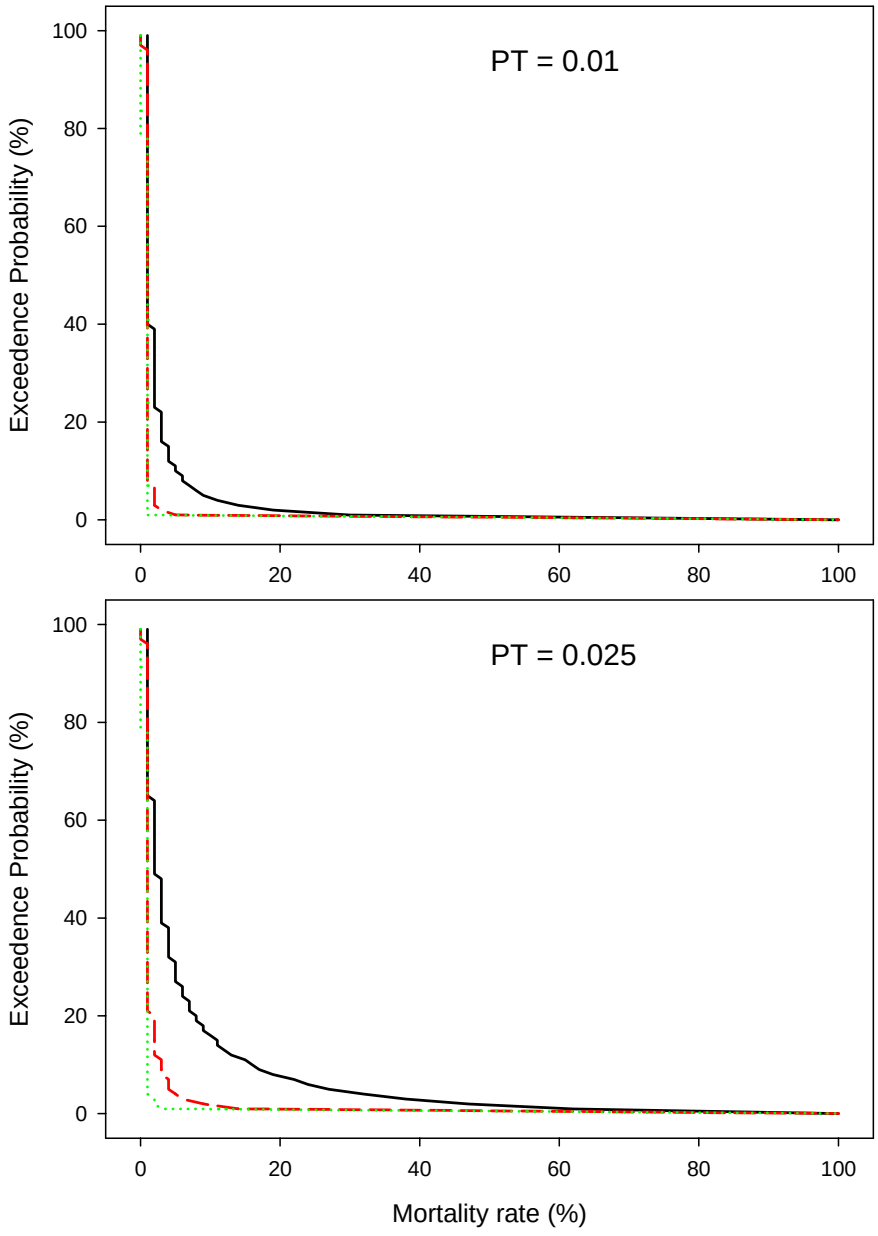


Figure 18. Risk curves for red fox.

Each plot shows lines representing assumptions of low sensitivity (dotted line), median sensitivity (dashed line), and high sensitivity (solid line).

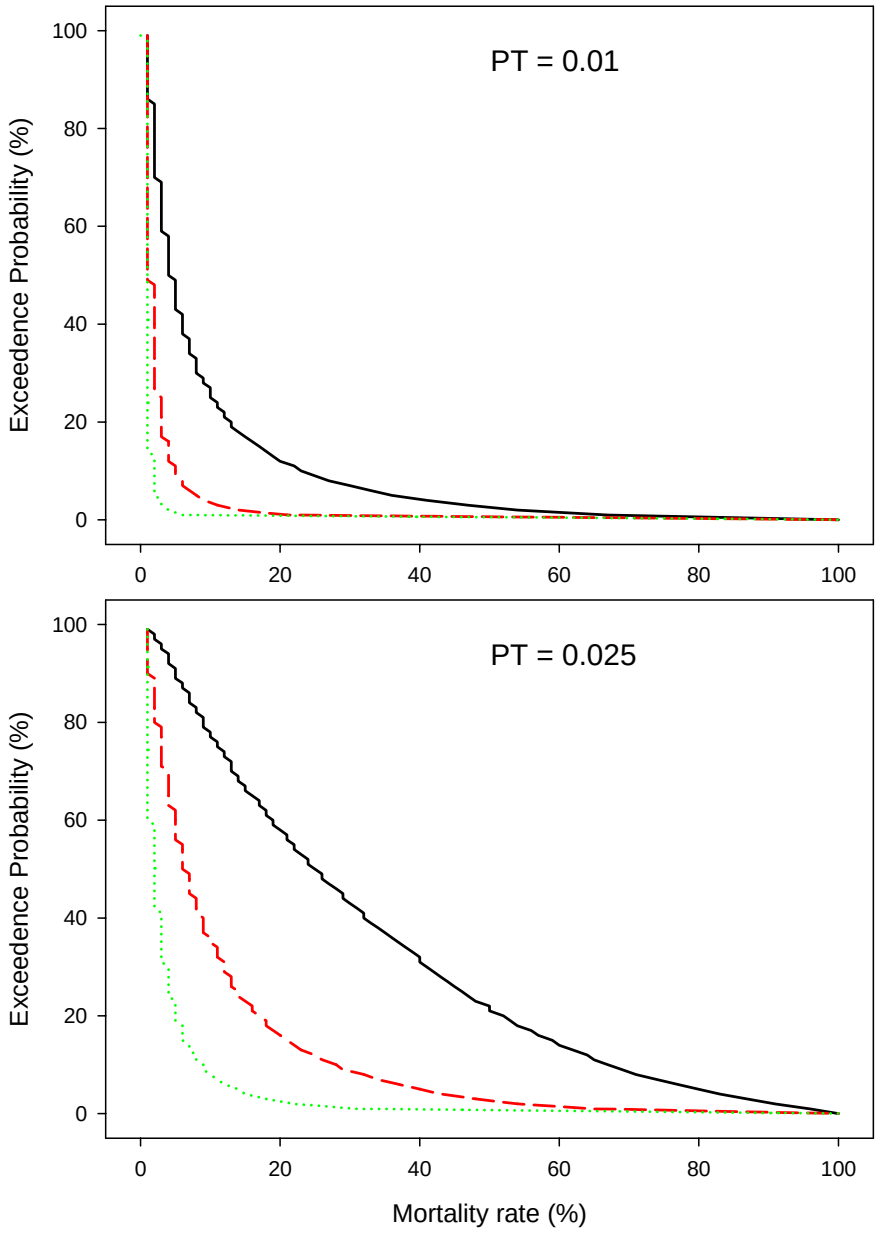


Figure 19. Risk curves for kit fox.

Each plot shows lines representing assumptions of low sensitivity (dotted line), median sensitivity (dashed line), and high sensitivity (solid line).

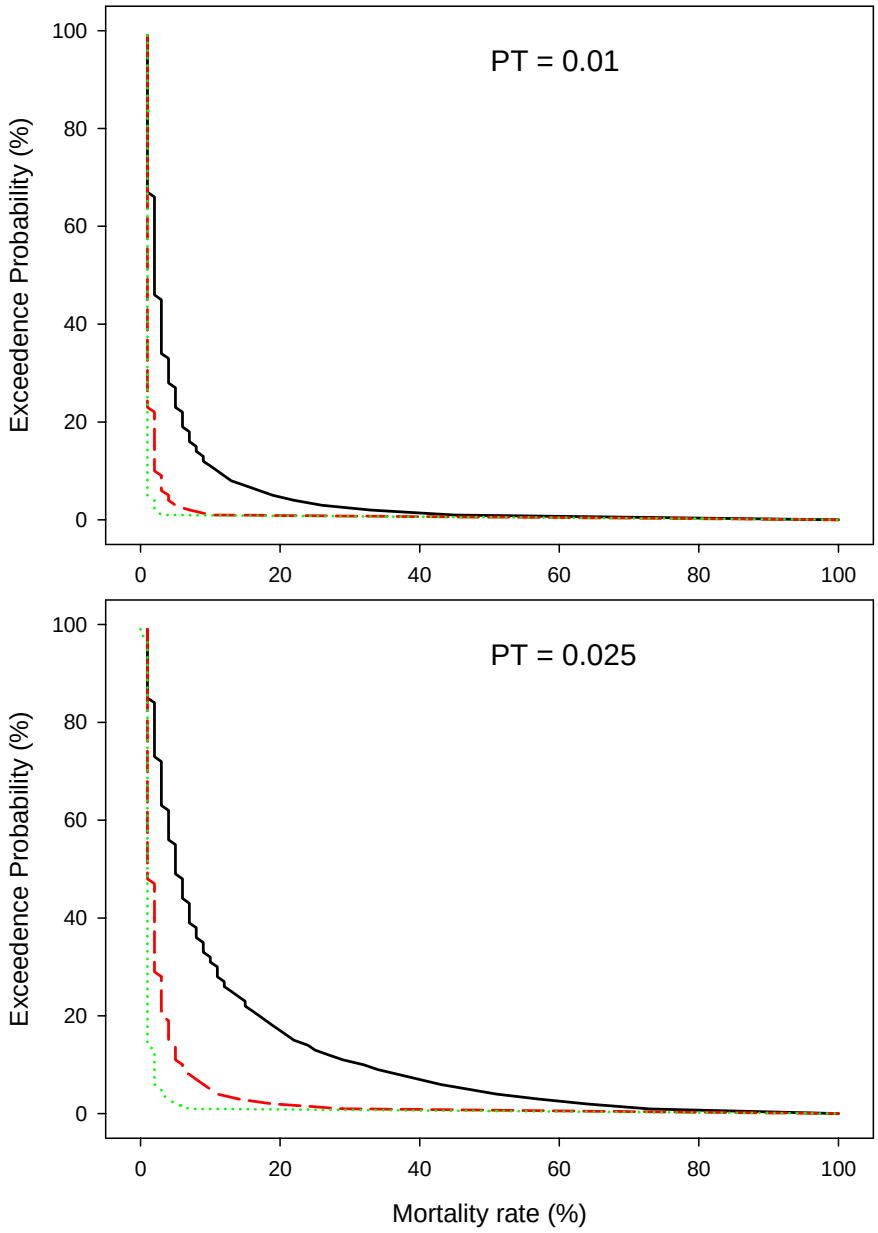


Figure 20. Risk curves for red-tailed hawk.

Each plot shows lines representing assumptions of low sensitivity (dotted line), median sensitivity (dashed line), and high sensitivity (solid line).

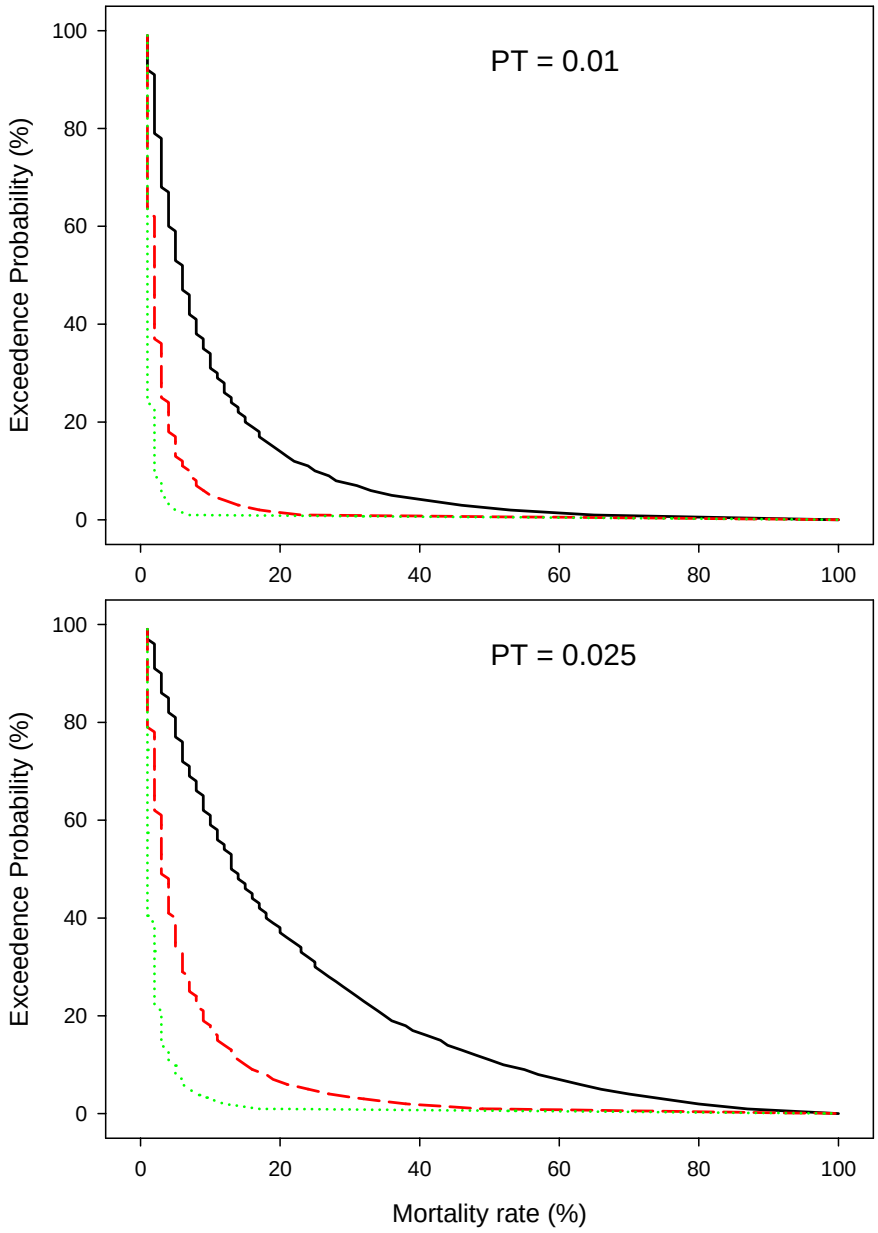


Figure 21. Risk curves for great horned owl.

Each plot shows lines representing assumptions of low sensitivity (dotted line), median sensitivity (dashed line), and high sensitivity (solid line).

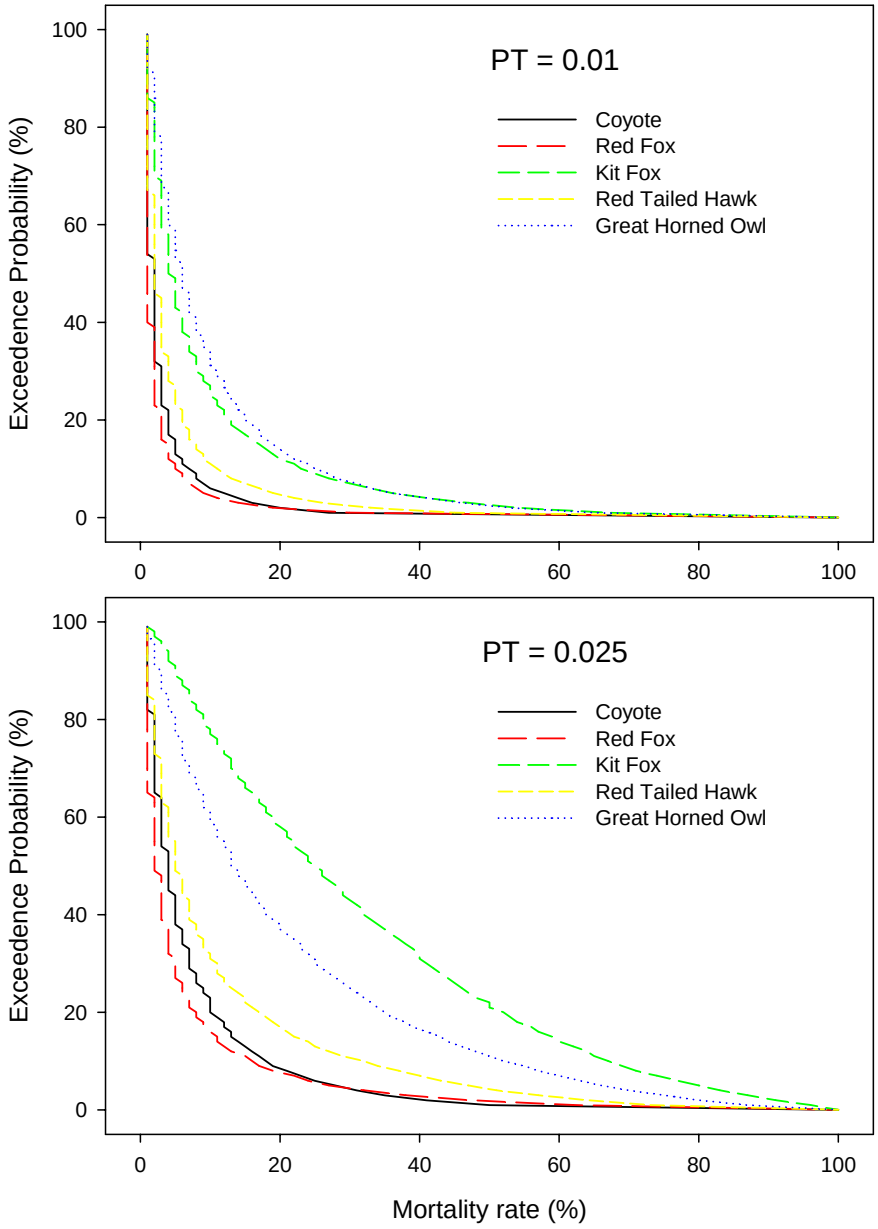


Figure 22. Comparison of risk curves for five predator species, assuming each species is highly sensitive to brodifacoum.

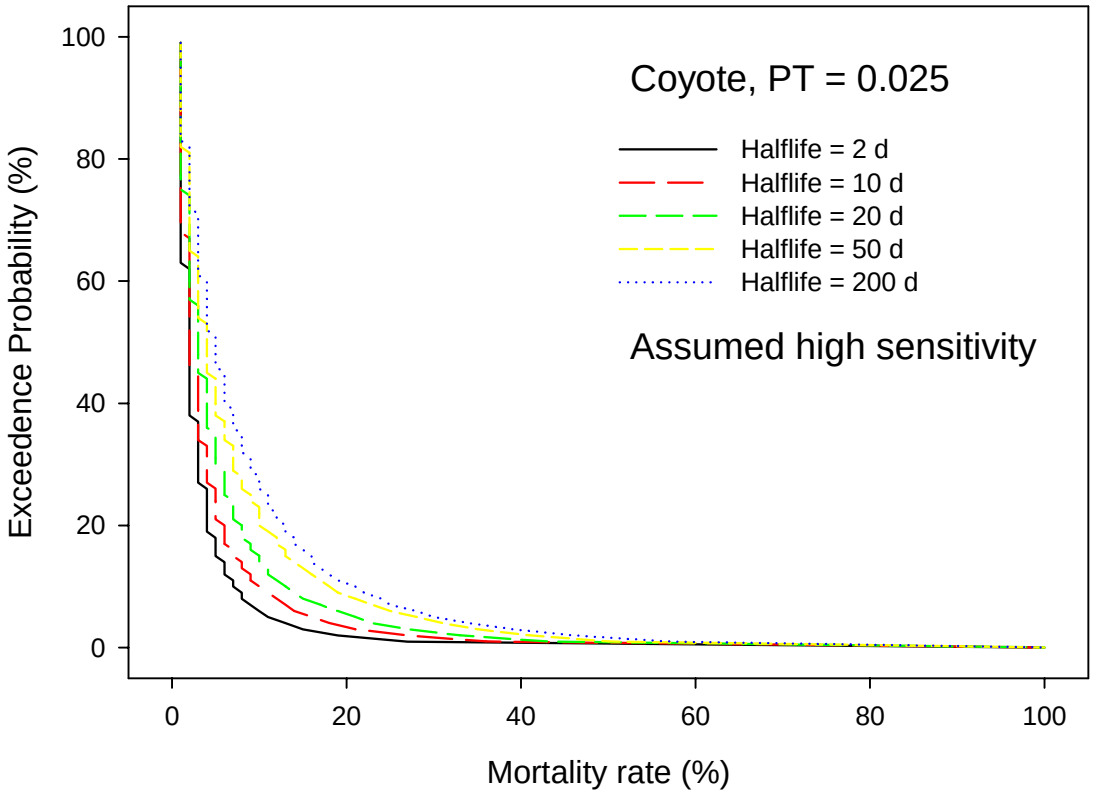


Figure 23. Risk curves for coyote (assuming high sensitivity, PT = 0.025) under different assumptions about depuration halflife.

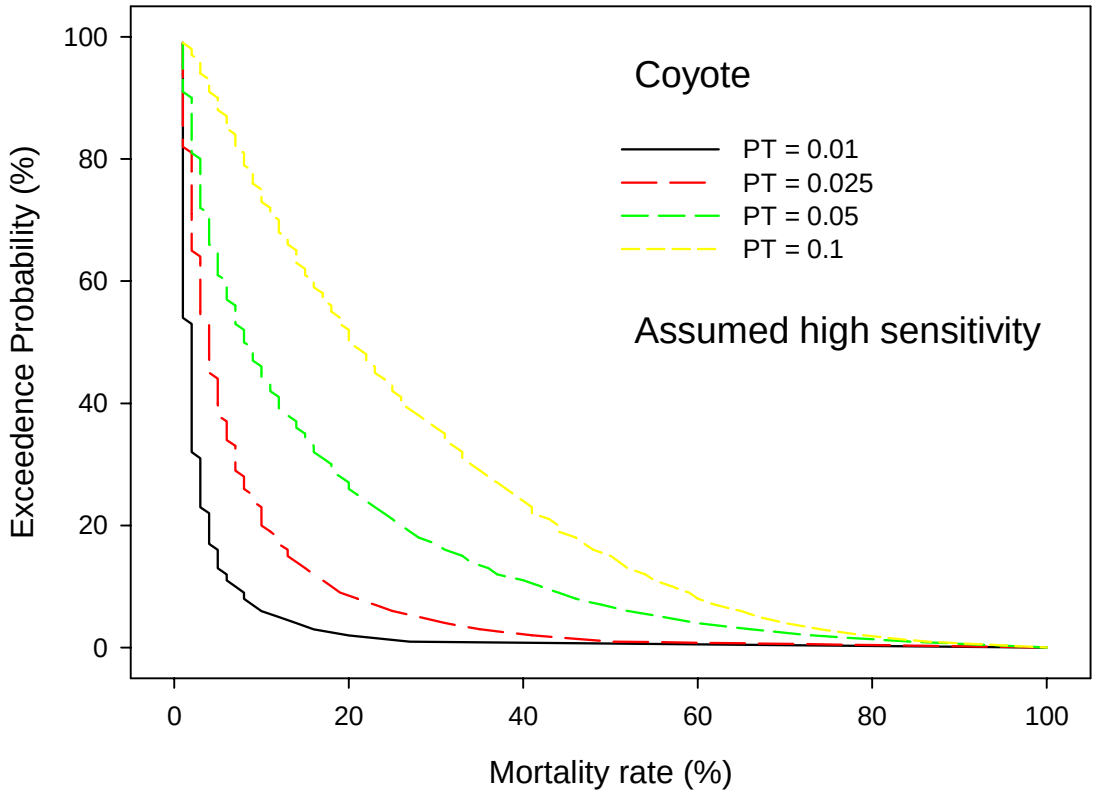


Figure 24. Risk curves for coyote (assuming high sensitivity) under different assumptions about PT, the proportion of rodents in the diet that have been exposed to brodifacoum.

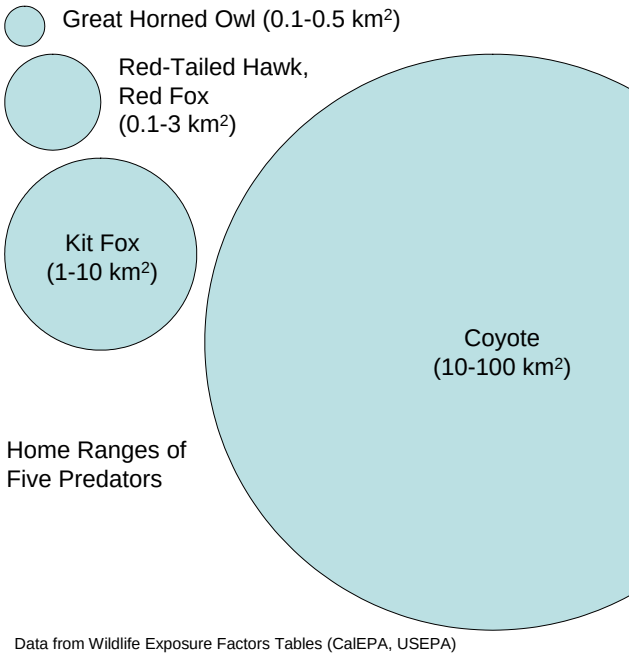


Figure 25. Home ranges of coyote, red fox, kit fox, red-tailed hawk, and great horned owl.

Circles are drawn proportional to upper limit of home range area for each species. Home range for each species tends to be smaller in urban environments than rural environments.

Appendix A. Summary of Dietary Composition Studies

Table 17. Summary of coyote dietary composition studies.

Rural/ Urban/ Suburban	State/ Province	Habitat	Time	Sample Type	Endpoint	% Rodents	Reference
R	CO	prairie	Nov	scat	vol	6	Gese et al. 1988
R	CO	prairie	Oct	scat	vol	7	Gese et al. 1988
R	CO	prairie	Nov	scat	vol	10	Gese et al. 1988
R	CO	prairie	Oct	scat	vol	14	Gese et al. 1988
R	AB	forest, bog, marsh	fall	stomach	vol	26	Nellis and Keith 1976
R	CO	prairie	Oct	scat	vol	26	Gese et al. 1988
R	CO	prairie	Nov	scat	vol	37	Gese et al. 1988
R-U	BC		fall	scat	vol	63	Atkinson and Shackleton 1991
R-U	BC		fall	scat	vol	66	Atkinson and Shackleton 1991
R	AB	forest, bog, marsh	spring	stomach	vol	16	Nellis and Keith 1976
R	CO	prairie	Apr	scat	vol	23	Gese et al. 1988
R	CO	prairie	Apr	scat	vol	24	Gese et al. 1988
R	CO	prairie	Apr	scat	vol	25	Gese et al. 1988
R	CO	prairie	May	scat	vol	34	Gese et al. 1988
R	CO	prairie	May	scat	vol	38	Gese et al. 1988
R	CO	prairie	May	scat	vol	50	Gese et al. 1988
R	CO	prairie	Apr	scat	vol	60	Gese et al. 1988
R	CO	prairie	May	scat	vol	63	Gese et al. 1988
R-U	BC		spring	scat	vol	68	Atkinson and Shackleton 1991
R-U	BC		spring	scat	vol	79	Atkinson and Shackleton 1991
R	CA	Tahoe National Forest	spring	scat	vol	80	Hawthorne 1972
R	QE	boreal forest	June	scat	vol	0	Samson and Crete 1997
R	QE	boreal forest	Aug	scat	vol	1.5	Samson and Crete 1997

Table 17. Summary of coyote dietary composition studies. (continued)

Rural/ Urban/ Suburban	State/ Province	Habitat	Time	Sample Type	Endpoint	% Rodents	Reference
R	QE	boreal forest	Aug	scat	vol	1.9	Samson and Crete 1997
R	CO	prairie	Sep	scat	vol	3	Gese et al. 1988
R	CO	prairie	Aug	scat	vol	5	Gese et al. 1988
R	QE	boreal forest	July	scat	vol	5.9	Samson and Crete 1997
R	QE	boreal forest	July	scat	vol	6.3	Samson and Crete 1997
R	CO	prairie	Sep	scat	vol	9	Gese et al. 1988
R	CO	prairie	Aug	scat	vol	15	Gese et al. 1988
R	CA (6)	coastal	summer -fall	scat	rel. freq	17.8	Rose and Polis 1998
R	CO	prairie	Jul	scat	vol	19	Gese et al. 1988
R	CO	prairie	Jun	scat	vol	19	Gese et al. 1988
R	IA	crops, pasture, woodlands	summer	scat	vol	19.5	Andrews and Boggess 1978
R	CA	foothill woodland	summer -fall	scat	rel. freq	20	Barrett 1983
R	CO	prairie	Jul	scat	vol	20	Gese et al. 1988
R	CA (7)	coastal	summer -fall	scat	rel. freq	21.2	Rose and Polis 1998
R	CA (5)	coastal	summer -fall	scat	rel. freq	21.7	Rose and Polis 1998
R	CO	prairie	Jun	scat	vol	23	Gese et al. 1988
	IA		spring-summer	scat	vol	24.6	Mathwig 1973
R	CO	prairie	Jul	scat	vol	26	Gese et al. 1988
R	CO	prairie	Aug	scat	vol	26	Gese et al. 1988
R	CO	prairie	Sep	scat	vol	26	Gese et al. 1988
R	CO	prairie	Jun	scat	vol	26	Gese et al. 1988
R	QE	boreal forest	Jun	scat	vol	28	Samson and Crete 1997
R	CA	Tahoe National Forest	summer	scat	vol	30	Hawthorne 1972

Table 17. Summary of coyote dietary composition studies. (continued)

Rural/ Urban/ Suburban	State/ Province	Habitat	Time	Sample Type	Endpoint	% Rodents	Reference
R	CA (3)	forest, desert	summer -fall	scat	rel. freq	31.7	Rose and Polis 1998
R	CA (2)	forest, desert	summer -fall	scat	rel. freq	32	Rose and Polis 1998
R	AB	forest, bog, marsh	summer	stomach	vol	35	Nellis and Keith 1976
R	CO	prairie	Jun	scat	vol	37	Gese et al. 1988
R	CA (8)	coastal	summer -fall	scat	rel. freq	41.7	Rose and Polis 1998
R	CA (4)	forest, desert	summer -fall	scat	rel. freq	52.6	Rose and Polis 1998
R	CA (1)	forest, desert	summer -fall	scat	rel. freq	56.5	Rose and Polis 1998
R-U	BC		summer	scat	vol	62	Atkinson and Shackleton 1991
R-U	BC		summer	scat	vol	73	Atkinson and Shackleton 1991
R	MN		winter	stomach	weight	1.6	Berg and Chesness 1978
R	MN		winter	stomach	weight	1.7	Berg and Chesness 1978
R	MN		winter	stomach	weight	2.1	Berg and Chesness 1978
R	MN		winter	stomach	weight	2.4	Berg and Chesness 1978
	IA		winter	stomach	vol	2.9	Mathwig 1973
R	CO	prairie	Feb	scat	vol	4	Gese et al. 1988
R	MN		winter	stomach	weight	4.3	Berg and Chesness 1978
R	MN		winter	stomach	weight	4.7	Berg and Chesness 1978
R	CA	Tahoe National Forest	winter	scat	vol	5	Hawthorne 1972
R	CO	prairie	Jan	scat	vol	5	Gese et al. 1988
R	MN		winter	stomach	weight	6.3	Berg and Chesness 1978

Table 17. Summary of coyote dietary composition studies. (continued)

Rural/ Urban/ Suburban	State/ Province	Habitat	Time	Sample Type	Endpoint	% Rodents	Reference
R	AB	forest, bog, marsh	winter	stomach	vol	8	Nellis and Keith 1976
R	CO	prairie	Mar	scat	vol	8	Gese et al. 1988
S	CA		Dec	scat	rel. freq	8.3	MacCracken 1982
R	CO	prairie	Feb	scat	vol	9	Gese et al. 1988
R	CO	prairie	Dec	scat	vol	10	Gese et al. 1988
R	CO	prairie	Mar	scat	vol	10	Gese et al. 1988
R	MN		winter	stomach	weight	10.9	Berg and Chesness 1978
R	IA	crops, pasture, woodlands	winter	stomach	vol	12.3	Andrews and Boggess 1978
R	CO	prairie	Dec	scat	vol	13	Gese et al. 1988
R	CO	prairie	Jan	scat	vol	13	Gese et al. 1988
R	CO	prairie	Feb	scat	vol	14	Gese et al. 1988
R	CO	prairie	Mar	scat	vol	14	Gese et al. 1988
	IA		winter	stomach	vol	14.6	Mathwig 1973
R	TX		winter	scat	rel. freq	24	Windberg and Mitchell 1990
R	TX		winter	scat	rel. freq	27	Windberg and Mitchell 1990
R	TX		winter	scat	rel. freq	31	Windberg and Mitchell 1990
R	TX		winter	scat	rel. freq	31	Windberg and Mitchell 1990
R	TX		winter	scat	rel. freq	36	Windberg and Mitchell 1990
R	TX		winter	scat	rel. freq	37	Windberg and Mitchell 1990
R	CA	foothill woodland	winter-spring	scat	rel. freq	45	Barrett 1983
R	CO	prairie	Dec	scat	vol	45	Gese et al. 1988
R	TX		winter	scat	rel. freq	50	Windberg and Mitchell 1990
R	CO	prairie	Feb	scat	vol	53	Gese et al. 1988

Table 17. Summary of coyote dietary composition studies. (continued)

Rural/ Urban/ Suburban	State/ Province	Habitat	Time	Sample Type	Endpoint	% Rodents	Reference
R	TX		winter	scat	rel. freq	55	Windberg and Mitchell 1990
R	CO	prairie	Jan	scat	vol	56	Gese et al. 1988
R	CO	prairie	Mar	scat	vol	56	Gese et al. 1988
R-U	BC		winter	scat	vol	82	Atkinson and Shackleton 1991
R	CO	woodland	year-round	scat	weight	5	MacCracken 1981
R	CA	open woodland		scat	weight	11.7	Fitch 1947a
R	CO	shrub-steppe	year-round	scat	weight	23	MacCracken 1981
R	CO	salt desert	year-round	scat	weight	25	MacCracken 1981
R	ID		summer-fall-winter	scat	weight	46.3	Johnson and Hansen 1979

Table 18. Summary of red fox dietary composition studies.

Rural/ Urban/ Suburban	State/ Province	Habitat	Time	Sample Type	Endpoint	% Rodents	Reference
	NY		late fall-winter	stomach	vol	32.2	Hamilton 1935
	MD		fall-winter	stomach	weight	17.6	Hockman and Chapman 1983
R	MI	forest	spring	scat	rel. freq	30.8	Johnson 1970
R	MI	forest	summer	scat	rel. freq	28.6	Johnson 1970
R	MI	forest	fall	scat	rel. freq	12.6	Johnson 1970
R	MI	forest	winter	scat	rel. freq	26.8	Johnson 1970
R	IL	woodland, agriculture		stomach	weight	21.6	Knable 1970
	MO	various	spring	stomach	weight	24.2	Korschgen 1959
	MO	various	summer	stomach	weight	6.2	Korschgen 1959
	MO	various	fall	stomach	weight	21.3	Korschgen 1959
	MO	various	winter	stomach	weight	22.5	Korschgen 1959
	MN		winter	stomach	weight	19.0	Kuehn and Berg 1981
R	MD	wildlife ref	fall		vol	28	Llewellyn and Uhler 1952
R	MD	wildlife ref	winter		vol	48	Llewellyn and Uhler 1952
R	MA	forest		stomach	vol	15.8	MacGregor 1942
	WI		winter	stomach	weight	2	Pils and Martin 1978
	WI		winter	stomach	weight	4	Pils and Martin 1978
	WI		March-July		weight	7.4	Pils and Martin 1978
R	WI	farm, pasture, woods	winter	prey	weight	4.5	Pils and Martin 1978
	NE			stomach	vol	21.4	Powell and Case 1982
R	ND	prairie farmland		stomach	vol	23	Sargeant et al. 1986

Table 19. Summary of kit fox dietary composition studies.

Rural/ Urban/ Suburban	State/ Province	Habitat	Time	Sample Type	Endpoint	% Rodents	Reference
R	UT	desert	winter	stomach	rel. freq	20.5	Smith 1978
R	CA	scrub, grassland	wet	scat	rel. freq	47.2	White et al. 1996
R	CA	scrub, grassland	wet	scat	rel. freq	46.1	White et al. 1996
R	CA	scrub, grassland	wet	scat	rel. freq	55.4	White et al. 1996
R	CA	scrub, grassland	dry	scat	rel. freq	49.3	White et al. 1996
R	CA	scrub, grassland	dry	scat	rel. freq	48.3	White et al. 1996
R	CA	scrub, grassland	dry	scat	rel. freq	48.8	White et al. 1996
R	CA	scrub, grassland	dry	scat	rel. freq	49.6	White et al. 1996
R	CA			scat	rel. freq	89.9	Paveglio and Clifton 1988
R	CA			scat	rel. freq	53.1	Logan et al. 1992
R	CA			scat	rel. freq	20.2	Scrivner et al. 1987
	CA	edge of range	winter	scat	vol	67.0	Orloff et al. 1986
	CA	edge of range	spring	scat	vol	88.0	Orloff et al. 1986
	CA	edge of range	fall	scat	vol	63.0	Orloff et al. 1986
	CA	edge of range	summer	scat	vol	95.0	Orloff et al. 1986

Table 20. Summary of red-tailed hawk dietary composition studies.

Rural/ Urban/ Suburban	State/ Province	Habitat	Time	Sample Type	Endpoint	% Rodents	Reference
R	Alberta	farm & woodlands	summer	prey	weight	40.3	Adamcik et al. 1979
R	OR	pasture & fields	Mar-Jun	prey	weight	63.0	Janes 1984
R	CA	foothills	spring-summer	prey	weight	65.1	Fitch et al. 1946
R	NJ,NY, CT	forest		remains, pellet	rel. freq	53.1	Bosakowski and Smith 1992
R	MI	fields, woodlots		pellet	rel. freq	93.1	Craighead and Craighead 1956
R	WY	grassland, forest	spring-summer	nest, pellet	rel. freq	86.2	Craighead and Craighead 1956
R	MI	fields, woodlots	May-Jun	nest, pellet	rel. freq	65.5	Craighead and Craighead 1956
R	CA	foothills	year-round	pellet	weight	56.9	Fitch et al. 1946
R	WI	farm, wetlands		nest	rel. freq	21.0	Gates 1972
R	WY	sagebrush	Apr-Aug	pellet	weight	32.8	MacLaren et al. 1988
R	AZ	desert		nest	rel. freq	20.0	Mader 1978
R	ID	shrub-steppe	breeding season	nest, pellet	rel. freq	41.9	Steenhof and Kochert 1985
R	ID	shrub-steppe	breeding season	nest, pellet	rel. freq	34.6	Steenhof and Kochert 1985

Table 21. Summary of great horned owl dietary composition studies.

Rural/ Urban/ Suburban	State/ Province	Habitat	Time	Sample Type	Endpoint	% Rodents	Reference
	ND		June	nest	rel. freq	11.3	Murphy 1997
R	CA	Paoha Is.	Aug, Apr	pellet	rel. freq	68.6	Aigner et al. 1994
R	CA	Negit Is.	May, June	pellet	rel. freq	70.5	Aigner et al. 1994
R	CA	fields, cliffs	June-July	pellet	rel. freq	95.4	Rudolph 1978
R	WA	agriculture. shrub-steppe	Oct-Jun	pellet	weight	65.0	Knight and Jackman 1984
	ID		nesting season	pellet	weight	41.5	Marti and Kochert 1996
	WY		spring	nest	rel. freq	91.9	Craighead and Craighead 1969
	MI		winter	pellet	rel. freq	86.2	Craighead and Craighead 1969
R	CA	chapparal		pellet	rel. freq	97.7	Cunningham 1960
S	CA	UCLA campus		pellet	rel. freq	82.4	Cunningham 1960
R	CA	grassland, chapparal	Nov-May	pellet	weight	29.1	Fitch 1947b

VOLUME ____ OF ____ OF SUBMISSION

BRODIFACOUM (PP581): ASSESSMENT ADDENDUM

TITLE

A Probabilistic Assessment of the Risk of Brodifacoum
To Non-target Predators and Scavengers
(MRID 46360601)

DATA REQUIREMENT

Not Applicable

AUTHORS

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COMPLETION DATE

August 2, 2007

PERFORMING LABORATORY

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LABORATORY STUDY IDENTIFICATION

Syngenta Number T001270-04

SUBMITTER/SPONSOR

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VOLUME 1 OF 1 OF STUDY

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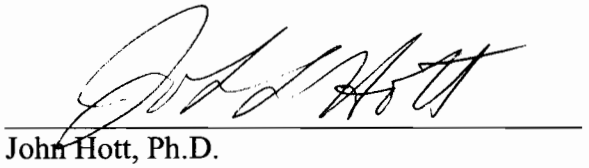
Since this report is a response to EPA Memorandum of August 24, 2005, EFED Evaluation of "A Probabilistic Assessment of the Rick of Brodifacoum to Nontarget Predators and Scavengers", a Good Laboratory Practice Compliance Statement is not appropriate for this volume.

Study Director: There is no GLP study director for this volume.



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2 August 2007
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Response to EPA Memorandum of August 24, 2005, EFED Evaluation of "A Probabilistic Assessment of the Risk of Brodifacoum to Nontarget Predators and Scavengers"

Jeffrey Giddings, Compliance Services International
William Warren-Hicks, EcoStat

Introduction

In September, 2004, a probabilistic ecological risk assessment (PERA) estimating the risk of brodifacoum to nontarget predators was submitted to the U.S. EPA by Syngenta Crop Protection on behalf of a group of rodenticide registrants (Syngenta Crop Protection, Bell Laboratories, LiphaTech, and Reckitt-Benckiser). The PERA was prepared by Jeffrey Giddings and William Warren-Hicks, who were employed by The Cadmus Group at the time the work began. In August, 2005, the EPA Office of Pesticides Environmental Fate and Effects Division (EFED) issued an evaluation of the PERA. The responses of Drs. Giddings and Warren-Hicks to EFED's evaluation are presented below. The responses are presented in the order that EFED's comments appeared in the evaluation. Excerpts from EFED's comments are quoted directly at the beginning of each response and are indicated by bold italic font.

(Note: EFED's document referred to the PERA as "the C/BR document," presumably reflecting Cadmus and the brodifacoum registrants as the sources of the assessment.)

1. Problem Formulation

General Conceptual Model

1.1. ***"Although it was included in the initial draft of the problem formulation for the C/BR probabilistic assessment, primary exposure to nontarget animals that ingest bait was omitted in the final assessment."*** (EFED p. 2) Our reasons for excluding primary exposure from the scope of the assessment are explained in the report (PERA p. 12) and are summarized in EFED's review (p. 2). We acknowledge this limitation of the scope of the PERA, and we do not claim that the PERA addresses risk to non-target bait feeders. EFED fails to consider the "practical and conceptual considerations" (PERA p. 12) that led to this decision. EFED does not deny our assertions that secondary exposure is of greater concern to regulators, nor that assessment of primary exposure will require "a fundamentally different exposure model" than the model used in the PERA. EFED does not refute these considerations, but apparently disregards them as reasons for excluding primary exposure from the PERA. EFED also disagrees with our assertion that primary exposure "is essentially a matter of bait station design and placement" (PERA p. 12), but they suggest no other factors that might affect primary exposure.

1.2. ***"The initial problem formulation indicated that three scenarios would be considered: urban, suburban, and rural. Those scenarios were not addressed in the CB/R assessment,***

nor were any aspects of spatial or temporal variability." (EFED p. 2) Although potential differences between urban, suburban, and rural environments were not explicitly represented in the model, such differences, as well as aspects of spatial and temporal variability, were addressed (PERA p. 13-14). The report explains in detail why the initial objective of simulating urban, suburban, and rural scenarios was not carried out. Variables expected to result in differential risk in the three scenarios are listed. "However, because very little information on these factors was available, the model as it was finally implemented was not habitat-specific. In the absence of data, distinctions between exposure in urban, suburban, and rural habitats would have to be based on assumptions. While these factors were not represented explicitly in the exposure model, assumptions about their overall impact on frequency of encounters with brodifacoum-containing food were represented by the variable PT" (PERA p. 14). Spatial and temporal variability, though not explicitly represented in the model, are also discussed, and options for incorporating data on spatial and temporal variability through representation of model parameters are considered (PERA p. 40).

1.3. ***"The C/BR assessment of risks to predators examined exposure from ingestion only and, for the most part, ingestion of only Norway rats."*** (EFED p. 2) The focus on dietary exposure is discussed and justified in the report (PERA p. 11). Reasons are presented for concluding that exposure of predators and scavengers through soil (dermal contact or ingestion), drinking water, and inhalation are insignificant compared to dietary exposure. The comment that the assessment examined ingestion of only Norway rats is inconsistent with the formulation of the model, which specifies PD (percent of rodents in the diet) and PT (percent of rodents in the diet that have been exposed to brodifacoum) but makes no distinction between Norway rats, other target rodents, and non-target rodents.

1.4. ***"Many predators and scavengers feed on those dead or dying birds that eat bait. For example, red-tailed hawks will prey on other birds (e.g. morning [sic] doves and starlings) which could be exposed to bait directly through the consumption of insects."*** (EFED p. 2) This comment confuses two issues. The first sentence considers secondary exposure of predators and scavengers that feed on bait-eating birds, while the "example" in the second sentence considers tertiary exposure from bait-eating insects to insectivorous birds to red-tailed hawks. (Note that the word "directly" in the quoted sentence should be "indirectly.") We acknowledge that the model considers only secondary exposure through feeding on bait-eating rodents (primarily target rodents, though this was not explicit in the model – see item 1.3), which is the exposure route of greatest concern for predators and scavengers.

1.5. ***"The C/BR assessment relies on a series of assumptions, which are not well documented and which lead to a large amount of uncertainty in the risk conclusions."*** (EFED p. 3) Any ecological risk assessment, in fact, relies on a series of assumptions; a significant limitation of EFED's previous deterministic assessment was the failure to objectify assumptions and quantify their effect. The "uncertainty in the risk conclusions" which applies to all assessments has two major sources: variability in factors considered in the model, and lack of knowledge about the mechanisms underlying the exposure and effects calculations. If assumptions and resulting uncertainty are cause to reject a risk assessment, then no assessment will be found acceptable.

EFED's use of the term "documented" in the quoted sentence is ambiguous. In the context of ecological assessment, the term often refers to identification and explication of assumptions; that is, one strives to clearly state ("document") the assumptions that have been made. We believe the PERA is clear in its statements of assumptions, so the first meaning is not what EFED intends, Alternatively, the term may refer to provision of scientific evidence to support a particular assumption, such as the proportion of rodents in a predator's diet. This evidence (or the lack thereof) is acknowledged and discussed in several places in the PERA. In cases where no supporting evidence could be found (such as the unknown value of PT) the PERA addresses uncertainty about parameter values by examining the model output from a range of assumed values.

1.6. ***"PD (the proportion of rodents in the diet) and PT 'are largely determined by the behavior of the focal species and the characteristics of the habitat,' but these factors are not considered in the model. Instead the assessment relied on LD50 values and average predator diets."*** (EFED p. 3) The first sentence quoted is correct: the model does not explicitly incorporate data and assumptions on many behavioral and ecological factors that could affect the model parameters. Instead, the Monte Carlo uncertainty method implicitly incorporates these factors into the sampling distributions. There is no need to develop a model to explicitly simulate these factors affecting PD because there is empirical data on the dietary composition of the surrogate species. This was explained in the report: "Initially we considered deriving estimates for PD and PT by simulating foraging behavior. However, a mechanistic model of predator and scavenger behavior could become extremely complex and involve many assumptions. We chose to use field data on dietary composition to estimate PD, rather than to reconstruct dietary composition through simulation of feeding behavior" (PERA p. 17). The data sources and limitations of the dietary composition data are thoroughly discussed in the PERA (pp. 23-24).

The second sentence quoted above is puzzling on two counts. First, LD50 values are irrelevant to the exposure model, including PD and PT. Second, the exposure model goes far beyond "average predator diets." The diet of each surrogate species is represented in the model by a distribution fitted to field data from as many as 98 studies. Furthermore, the model simulated variation in the diet of each individual from day to day.

2. Effects Analysis

Quality of Data

2.1. ***"The effects data were reviewed for quality only as it relates to the statistical aspects of the study. Methodological aspects of these studies were not examined. For example, the length of the study and supplemental vitamin K in the basal diet, both of which have been shown to affect toxicity of brodifacoum in laboratory tests, were not reported. Several of the avian tests were only available as sketchily described studies reported by Godfrey (1986)….Such data were not used to calculate risk quotients in EPA's deterministic assessment and should not be relied upon in other than a qualitative manner in a higher-tier assessment unless the uncertainty is accounted for."*** (EFED p. 3) We agree about the relevance of observation time, vitamin K regimen, and stress of captivity for the outcome of

laboratory toxicity tests with anticoagulants. Nevertheless, despite their limitations, dependencies, and uncertainties, the available data from standard toxicity studies provide the best (perhaps the only) source of information for characterizing the effects of brodifacoum.

We subjected all available toxicity test results to a rigorous set of quality assurance criteria (described on p. 18 of the report). As noted in EPA's comments, many of the criteria were developed to ensure a correctly specified statistical model. However, we note that the basic tenets of toxicology are reflected in the characteristics of the statistical model (e.g., monotonic dose-response relationships, maximization of between concentration responses, etc.). When information was available that provided insights into details of a particular toxicity test, we used that information in the selection process. However, we note that the resulting set of toxicity tests should be considered the "best" available information on brodifacoum effects, from both a biological and statistical perspective. The ability to quantify variation among tests from different investigators is an advantage for the analysis of the effects data. Our risk analysis is actually improved due the representative nature of the effects data chosen. Between-investigator differences represent the state of the knowledge of brodifacoum effects. Therefore, we believe that all effects data chosen for this analysis are appropriate, particularly given the objective of the risk assessment.

Sensitivity of Species

2.2. ***"Whereas it is typical to use the 5th and 95th percentiles as the extremes of the SSD, C/BR instead used the 10th and 90th percentiles as indicators of 'high' and 'low' sensitivity."*** (EFED p. 4) While use of the 5th and 95th percentiles may be EFED's preference, the variety of current scientific and regulatory interpretations of SSDs makes it difficult to establish that use of any particular set of SSD point estimates is "typical."

2.3. ***"Because LD50 values for three of the nine bird species used by C/BR fall below the 10th percentile dose-response curve, the 10th percentile is not representative of a highly sensitive species."*** (EFED p. 4) EPA is confusing the degree of interpretation afforded by the data with the proper interpretation of a probabilistic model. The model, by definition and assumption, represents the expected relationship between concentration and effects for all appropriate species (as defined by the species used to "train" or "parameterize" the probabilistic model). Data cannot be used to define percent effect beyond the explicit bounds of the data set. In practice, percent effect calculated from the data is strictly dependent upon sample size. The data are assumed to be representative of the species population of interest, however, the data are not assumed to be a perfect representation of the dose-effects relationship. Therefore, the assumption that the 10^{th} and 90^{th} percentiles are inappropriate due to the underlying training data set, is a completely incorrect interpretation of the model and the model parameterization process. In the risk assessment, the model predictions, not the training data, are used to define a highly sensitive species. The selection of a percentile for reporting purposes (i.e., the 10^{th} and 90^{th}) was based on expert opinion. There is nothing inherently appropriate about the 5^{th} and 95^{th} percentiles, and we point out that we are not attempting to implement a classical hypothesis test where the 5^{th} and 95^{th} are assumed (however incorrectly) to be viable decision endpoints in many contexts. We believe that the 10^{th} and 90^{th} percentiles are reasonable percentiles for reflecting highly sensitive species. Examination of the dose-response curves indicates that for most species, there is an

insignificant difference in concentration between the 90th and 95th percentiles or the 5th and 10th percentiles. Since the tails of the distribution are more difficult to estimate (i.e., require a larger sample size to estimate with the same precision as other areas under the dose-response curve), the 10th and 90th percentiles may more accurately reflect the response of sensitive species to brodifacoum.

2.4. ***"The available dietary (LC50) data and their potential impact on the species distributions should be discussed in the risk characterization, even if they were not used to generate the SSDs."*** (EFED p. 4) The PERA summarizes the reasons for excluding LC50 data from the assessment as follows: "Under current EPA test guidelines, the LD50 is argued to be a more appropriate risk assessment endpoint than the LC50 (Mineau et al. 1994; Mineau et al. 2001). Toxicity tests resulting in LC50s (a few studies, mainly with rats) were not used in this risk assessment. Likewise, exposure was calculated in terms of dose to the animal, not concentration in the diet. LC50 values can be converted to LD50s if assumptions are made about food ingestion during the test, but we considered that the uncertainty introduced by those assumptions would outweigh the loss of information caused by excluding LC50 data." (PERA p. 18-19) In light of these factors, the relevance of the limited available LC50 data to risk characterization in this assessment is unclear.

Representativeness of the Data

2.5. ***"EPA questions how representative the SSDs are for nontarget animals that may be exposed to brodifacoum in North America. Much of the data were generated in New Zealand in the 1970s and consisted of LC50s [sic; actually LD50s were used] for sheep, wallaby, European rabbit, Asian harrier hawk and other species not occurring in North America. Uncertainty…should be acknowledged and can be addressed, at least to some extent, using SSDs."*** (EFED p. 4) To our knowledge, there is no evidence that the sensitivity of birds and mammals to brodifacoum is related to their geographical location. The uncertainties related to extrapolation from tested species to the surrogates and other untested species are discussed in the PERA (p. 43-44). The possibility that North American species may differ from non-North American species in their overall sensitivity to brodifacoum is not mentioned in this discussion because such differences have not been demonstrated and would be at most a small contributor to the uncertainty about surrogate species sensitivity. The use of available toxicity test data to represent the sensitivity of untested species is always a source of uncertainty in ecological risk assessment of chemicals. The Bayesian hierarchical modeling used in the PERA is a powerful approach to incorporating all sources of variability in toxicity data (within tests, between tests with the same species, and among species) into the SSD analysis.

Canids as Surrogates

2.6. ***"The only basis for using 3 canids as surrogates for all mammalian predators and scavengers seems to be that some dietary data were readily available….Using other species besides canids (e.g., felid, mustelid) would have been more appropriate unless the assessment was intended solely to address risks to canids."*** (EFED p. 4-5) The criteria for selection of surrogate species are thoroughly presented in the PERA. "The main criterion for selection of surrogate species was a high presumed level of exposure, based on diet and habitat. Other criteria considered in selection of surrogate species included ecological

significance, cultural value, and incident reports." (PERA p. 15) The PERA goes on to explain that the five species were selected because "rodents comprised a significant component of the diet." The percentage of rodents in the diets of felids and mustelids is considerably lower than that of the canids selected. Percent rodents in the diet (PD) and body weight are the only species-specific parameters in the model. Therefore, the results obtained for the three canids apply to any non-herbivorous mammals of similar weight with similar (high) percentage of rodents in the diet. This is stated in the PERA: "By inference, the same conclusion applies to other species of birds and mammals with similar dietary composition and metabolism." (PERA p. 45)

3. Exposure Analysis

Limitations of the Residue Data – Pulsed Baiting

3.1. ***"The mean residue level in the 111 pulsed-bait rats was 1.6 ppm, versus 3.4 ppm in the 22 saturation-baited rats. These values are significantly different (t = -2.52, p<0.01) and clearly should not be pooled. Even if the data were not significantly different, there is no justification for using residue data from rats exposed to pulsed-baiting applications….Omitting the pulsed-baiting studies from the assessment would leave field data from only 22 rats exposed with any similarity to baiting practices in the U.S."*** (EFED pp. 5-6) EFED's calculations of the numbers of rats and mean residue levels do not agree with the data presented in the three studies in question, and we are unable to reproduce EFED's statistical results.

Edwards and Swaine (1983) reported results for carcasses of 25 rats exposed to saturation baiting with pellets. Six of these were from a farm where other anticoagulants were also in use, and EFED excluded these values from their analysis. This would leave 19 rats, not 22 as stated by EFED. Furthermore, the mean residue concentration of the 19 rats was 1.70 ppm, not 3.4 as stated. The page of the original report presenting the residue concentrations in individual rat carcasses is reproduced in Appendix A.

The other studies reported by Edwards et al. (1984a,b) presented results from field trials designed with pulsed baiting. However, at 4 of the 32 farms in the two studies, saturation baiting was practiced. Brodifacoum concentrations were presented for carcasses of 119 rats (not 111), including 20 from the saturation-baited farms. The mean residue concentration of the 119 rats was 1.86 ppm; excluding the 20 saturation-baited rats, the mean residue concentration was 1.55 ppm. If the results for the 20 saturation-baited rats are combined with the results for the 19 rats from the 1983 study, the mean residue concentration for saturation-baited rats was 2.59 ppm.

We have reanalyzed the data used in the PERA, with two modifications: (1) deletion of the 6 values for carcasses from the farm where other anticoagulants were in use (Edwards and Swaine 1983); (2) reassignment of 3 values from Farm I (Edwards et al. 1984b), one of the saturation-baited farms in the pulsed-baiting study, which were incorrectly classified as pulsed in the PERA. With the 6 values from Edwards and Swaine (1983) removed, we compared the 19 remaining saturation-baiting values with the 119 values reported from the

pulsed-baiting studies (Edwards et al. 1984a,b) using a t-test. The two groups were not significantly different ($t = 0.2453$, $p = 0.8086$, 21 df). When the 20 values from saturation-baited farms in the pulsed-baiting study were combined with the 19 values from the saturation-baiting study, a significant difference was detected ($t = 2.1412$, $p = 0.0376$, 46 df). In the PERA analysis, before the two data modifications mentioned, the difference was not significant ($t = 1.3181$, $p = 0.1933$, 51 df).

This re-analysis shows that residue concentrations in rat carcasses from the first (saturation-baiting) study are not significantly different from the concentrations in carcasses from the second and third (pulsed-baiting) studies. If the carcasses from the 4 saturation-baited farms in the second and third studies are pooled with the first study the difference becomes slightly significant ($p = 0.0376$). We agree that it would be inappropriate to pool the data from saturation-baited and pulsed-baited rats if a significant difference exists between the two groups. The sample size for saturation-baited rats is 39 (not 22), which we believe is sufficient to determine the distribution of residue concentrations for the exposure model. However, because the differences between saturation-baited and pulsed-baited rats (as well as mice and voles, which were included in the PERA distribution) are small, we do not expect the model results to be substantially influenced by the selection of residue data.

EFED's assertion that only the saturation-baiting study bears "any similarity to baiting practices in the U.S." (EFED p. 7) is not based on facts. A close reading of the 3 field studies (Edwards and Swaine 1983; Edwards et al. 1984a,b) shows that baiting practices did not vary consistently between supposedly saturation-baited and pulsed-baited farms. For example, at two of the farms in each of the pulsed-baiting studies (Edwards et al. 1984a,b) bait was replaced at less than the prescribed 7-d interval; in fact, baiting was ad lib at two of the farms for the first 2-3 weeks (Edwards et al. 1984a). Conversely, bait was replaced every 7 days at three of the farms in the saturation-baiting study (Edwards and Swaine 1983). More importantly, the quality of the baiting programs (adequacy of bait covering, quantity of bait placed, communication of instructions to operators) varied considerably among farms in all three studies. Furthermore, the studies included baiting in some areas that would not be allowed in the U.S., such as fields, hedgerows, and woods. Thus the baiting practices in all three studies differed in some respects from baiting practices in the U.S., and there is no justification for considering that one of the studies was representative of U.S. practices while the other two studies were not. It is also important to note that we found very little information about actual baiting practices in the U.S. In short, the data from the three field studies are the most representative data available, and use of these data (including the variability of brodifacoum concentrations among rats) reduces, rather than contributes to, the uncertainty of the assessment.

Residue Reporting Data

3.2. "The data from 13 rats captured alive and analyzed for brodifacoum residue in Edwards et al. (1984) was incorrectly reported as being '0.05 ppm (mg/kg),' which was the Limit of Detection for brodifacoum. By omitting the '<' and reporting the residue level as '0.05 mg/kg' for each of those rats, the assessment implies that a low level of residue was detected. This is probably not the case. In fact, if no residue was detected in 5 rats, it may indicate that the baiting program was not very efficacious or that the

rats had not yet eaten the bait." (EFED p. 7) Using the detection limit to represent concentrations below the detection limit is a common, conservative practice in environmental assessment. We agree that the "<" should have been shown in Table 4 for accuracy, but disagree with the implication that this was a deliberate effort to suggest that residues were detected in all rats. Whether the actual concentration in those rats was zero, the limit of detection, or some concentration in between is inconsequential for this assessment. Most importantly, the fact that brodifacoum concentrations were below the limit of detection in a substantial fraction of live rats trapped in this study supports our supposition that PT is relatively low, even in the vicinity of an active baiting program. The data from trapped rats also suggests that the distribution of carcass residue concentrations used in the exposure model may overestimate exposure to predators that feed on live rodents.

Limiting Assumptions for PD and PT

3.3. "Behavior and habitat are not addressed in the model. Instead, C/BR uses field data on dietary composition as reported in the literature. This may be a problem since most of the dietary studies in the literature were conducted in wild areas…devoid of commensal rats and mice, and thus commensal rodents comprised little if any of the diet." (EFED, p. 8) We agree that commensal rodents are likely to be insignificant components of predator diets in wild areas, but we used the field data to determine the fraction of all rodents, not just commensal rodents, in the diet. The model makes no distinction between commensal and non-commensal rodents in the diets of the surrogate species. One of the main points of our analysis, which EFED does not, is that predators have access to a wide range of rodents other than those that might be targets of a baiting program.

3.4. When a rodenticide bait is applied, the food supply is altered in two ways. The bait provides a supplemental food source for target and nontarget primary consumers, which in turn provides a source of dead and dying food for predators and scavengers. Opportunistic species, including the five surrogate species used in the model, may drastically alter their foraging behavior and food habits to exploit an abundant, even if ephemeral, food source….Incorporating feeding behavior and other aspects affecting it into the model may be more difficult than ignoring it, but it can be done." (EFED, p. 8) The interrelationships hypothesized in this comment are as complex as the entire PERA. Perhaps they can be incorporated into the model, but we believe these higher-level effects contribute less uncertainty than the major sources we have identified, such as the toxicokinetics of brodifacoum and the fraction of brodifacoum-contaminated prey in a predator's diet.

3.5. "In their submission of February 23, 2004, C/BR states that '…we will run the model using different assumptions based on direct estimates and expert opinion (including PT=1 as the worst case).' For some reason, high-exposure scenarios were not presented in the assessment….Results of exposure scenarios using PT values above 2.5% (e.g., 15%) were not included in the risk assessment even though C/BR acknowledged that they 'compared results of the daily dose model using PT values ranging form 1% to 15%.'" (EFED, p. 8) The results of daily dose model runs with coyote and PT values ranging from 1% to 15% are presented in Table 7 of the PERA. They demonstrate that the mean daily dose is directly proportional to PT over that range of values.

The same table also shows the sensitivity of daily dose to the mean PD and PD standard deviation.

3.6. "On p. 28 C/BR states that 'The proportion of Norway rats and house mice that are exposed to a brodifacoum baiting program is unknown, but is likely to be much smaller than one in ten.' The value of one in ten is unsupported and seems to postulate an ineffective baiting program – i.e., one in which only a small proportion of the target organisms will be exposed." (EFED, p. 9) Our estimate of a proportion of exposed rats and mice as "much smaller than one in ten" refers to the total population of Norway rats and house mice available to predators. Only a subset of the individuals in that population that are the direct targets of a brodifacoum baiting program. Among the direct targets, a much greater proportion would be exposed.

An analogy may clarify this point. The likelihood that a random San Franciscan will be hit by a trolley today are greatly increased if the individual is sitting on the track. The PERA estimates risk to the random San Franciscan, while EFED is concerned with the individual on the track. This discrepancy in understanding of the scope of the assessment was unfortunately not recognized during our discussions with EFED about the Problem Formulation.

3.7. "In the daily dose model, PT is implemented as a binomial distribution, where a value of 0 indicates that none of the rodents consumed contain brodifacoum and a value 1 indicates that all of the rodents consumed contain brodifacoum. All or nothing is an extreme scenario…The authors of the report appended to this review suggest the alternative approach of applying PT to individual prey meals rather than to total daily events…As they note, this gives a greater chance that at least one meal is contaminated, so there will be fewer days with doses of 0." (EFED, p. 9-10) The model could indeed be made more complex in the manner described. The effect of the proposed alternative would be to reduce the day-to-day variability in daily dose for each individual, without changing the mean daily dose. There would be fewer days with doses of 0, as suggested, but also fewer days with high doses. We have not explored the effect of this modification on the risk estimates, but we are not surprised by the finding (reported in EFED's review) that the two approaches yield the essentially the same result for values of PT below 20%, nor that the mean daily dose was unaffected even at higher PT values. See our response to Point 3.6 regarding the interpretation of PT values.

3.8. "Key to this alternative is the bioaccumulation potential of brodifacoum. The difference in modeling approaches (i.e., All or Nothing vs. Individual Prey methods) may be important if the half-life for elimination kinetics is moderate to long (> 10 days), as is the case for brodifacoum. The greater the frequency of consecutive days of non-zero exposure, the more brodifacoum can be expected to accumulate in the body of a predator or scavenger." (EFED, p. 10) We disagree with the last sentence of this comment. While we have not explored this feature of the model, we expect that the long-term accumulation of brodifacoum in the body will be primarily a function of the total amount of brodifacoum ingested over time, regardless of whether the ingestion takes place as a few large events or many small events. Moreover, because the "Individual Prey method" would

reduce the likelihood of receiving a large daily dose (though it would increase the likelihood of receiving a small daily dose), the maximum concentration of brodifacoum in the body over a period of time would be lower.

Distribution of 100 Means vs Distribution of 10,000 Exposure Events

3.9. "Section 3.4.4 of the report describes the approach, stating that 'The mean of the 100 simulation outcomes was calculated, and the 100 means (from 100 individuals) were plotted as reverse cumulative frequency distributions.' The risk characterization (Section 5.1), however, states, 'For each cumulative dose model run, the full set of 10,000 dose estimates (100 estimates for each of 100 individuals) was combined into a single exposure distribution reflecting both within-individual and among-individual variation.' While the statements are conflicting and the input files were not included in the materials provided, it appears from code and from certain descriptive statistics that the C/BR assessment elected Option 1, with the summary statistic being the arithmetic mean of the 90-day maxima." (EFED, p. 11) There is no conflict between the statements quoted from Section 3.4.4 and Section 5.1. Section 3.4.4 summarizes the results of the cumulative dose model, while Section 5.1 describes the procedure used to generate the risk curves. In both cases, the process was exactly as stated in the quoted passages. The 100 means were *plotted* in Figures 12, 13, and 14, and this is clearly stated in the figure captions. However, the full set of 10,000 estimates was used as input for the risk characterization.

90-day Time Period for Exposure

3.10. "The choice of a 90-day period appears to be arbitrary….The concept of first order kinetics implies that it may take some time for the chemical to achieve steady state. This time to steady state is influenced by both the choice of depuration halflife (t½) as well as the frequency of daily doses….When the dosing regimen is frequent, the assumption about t½ becomes critical; and the maximum 90-day body burden is unlikely to be captured by the first 90-days [sic] of the time series, especially for the longer halflife scenarios." (EFED, p. 11-12) The reason for selection of a 90-d simulation period was stated in the PERA (p. 33): "The choice of a 90-d simulation period ─ one season ─ was a practical decision made during model scoping." The consequences of extending the simulation period to 180 or 360 days were explored using halflives of 5, 50, and 200 days precisely to address the issue raised by EFED's comment, and the results were presented in Table 10 of the PERA. With a 50-d halflife (the value used for most simulations in the assessment), the mean and 90th percentile of the maximum dose after 360 days were approximately twice the 90-d values; with a 200-d halflife, the maximum cumulative dose was approximately three times the 90-d values.

Given the relatively infrequent ingestion of contaminated prey and the relatively long half-life, body burdens are not expected to reach a steady state. Furthermore, as stated above (Point 3.8), the frequency of ingestion has little bearing on body burden over a long period of time.

Kinetic Model

3.11. "Basing most of the analyses on a 50-day halflife in a simple one compartment model…will probably underestimate risk." (EFED, p. 12) The effect of varying the

halflife assumption was explored in the PERA (Section 3.4.4.1), and it was found that "dose distributions generated using the 50-d halflife were similar to those generated using 100-d and 200-d halflives (Table 8, Figure 12)." (PERA p. 33)

3.12. "The kinetics of brodifacoum can be described by a simple flow-limited physiologically based pharmacokinetic (PBPK) model that is optimized with concentration data in liver, kidney, and carcass." (EFED, p. 13) The PERA acknowledged the oversimplification of the one-compartment first-order model, and we agree that a more complex toxicokinetic model could be developed for brodifacoum. However, we stand by the statements quoted by EFED at the top of p. 12. Even a highly specific, well-parameterized simulation of brodifacoum flux between two or more internal compartments would not improve the risk assessment, for the simple reason that all of the available dose-response data are based on total body burden. At a workshop on rodenticide risk held in Montreal in November, 2006, it was evident that there is little understanding among experts about the relationship between brodifacoum concentrations in blood, liver, and whole body, and the resultant toxic effects.

Field and Incident Data

3.13. "There is an ongoing field project involving the San Joaquin kit fox, one of C/BR's surrogate species, that could have provided more relevant and useful information than the few dietary studies C/BR gleaned from the open literature. Also in California, researchers … have studied the ecology and behavior of coyotes (also a surrogate species)….They captured and radiocollared numerous coyotes, bobcats, and mountain lions and determined home ranges in relation to human development. Many of these individuals were exposed to anticoagulant rodenticides, including brodifacoum." (EFED, p. 13) We appreciate the information EFED provides concerning these studies, and agree that additional field data on the dietary composition of these species, especially in areas near human development, would be useful in the risk model. It is unclear how data on ecology, behavior, and home range would be relevant to the model. We also note that the PERA used not "a few dietary studies" but a total of 158 studies, including 15 on the San Joaquin kit fox and 98 on the coyote, and these data were not "gleaned from the open literature" but taken from the EPA Wildlife Exposure Factors Handbook and the Cal/Ecotox Exposure Factors tables, two standard data sources for wildlife risk assessment.

3.14. "The C/BR risk characterization could include an explanation of the incident data that are available on brodifacoum." (EFED, p. 13) We agree that incident data would be useful for comparison with and interpretation of the results of the PERA.

4. Risk Characterization

Implementation

4.1. "While employing a Bayesian hierarchical framework is an interesting and potentially useful innovation, the use of such a model is not a substitute for limited, incomplete, and inconsistent data." (EFED p. 14) We agree that the Bayesian framework is not a substitute for good data, and we did not suggest this in our document. The Bayesian

framework allows an explicit mathematical/probabilistic method for pooling information from multiple sources, without any loss of information inherent in the existing data sets. Therefore, the information content of a "data weak" source is informed by information from other sources. We believe that this issue arises frequently in risk estimation. In this way, the Bayesian framework provides a mathematically defined and rigorous theoretical advantage over other methods.

4.2. Using the 10th percentile to represent sensitive species "appears to limit severely the resulting overall effects distribution." Many species seem to fall outside the 80% confidence bounds. "This implementation of the hierarchical approach appears to restrict, rather than encompass or expand, the range of outcomes expected." (EFED p. 14-15) See our response to point 2.3 above. In addition, we note that by pooling information from multiple species using the entire dose-response curve (rather than selecting a single model-based endpoint such as the LD50 and building an SSD in the standard sense), we have incorporated a great deal of information that is lost with traditional approaches. Therefore, the resulting risk curve is estimated with greater precision than is possible with the standard SSD methods. The interpretation of the resulting curve is a reflection of the information content of the data.

4.3. "Distribution assumptions for both the model parameters of the overall distribution and for the individual species dose-response curves should have been discussed.…Using the logistic model rather than probit "may underestimate mortality at the lower end of the curves." EFED (p. 15) First and foremost, the probit model (which is a reflection of the normal distribution with the mean and variance assumed known) is inappropriate for binary response variables (e.g., life/death, see Warren-Hicks 2002[1] for an appropriate derivation of a probabilistic model for binary responses). Therefore, a correctly formulated model must reflect the binary nature of the data, and the selection of a probability distribution must follow from this argument. In our model, the cumulative logistic function is "linked" to the expected probability of survival (which is reflective of the binary response). When investigators attempt to fit a probit model to binary data, they effectively transform the measurements into a different metric. This exercise in turn results in a biased estimate of the distribution variance.

Second, even if one incorrectly accepts the assumption that the probit model is appropriate, a resulting comparison of the tails of the distribution typically indicates little practical difference. Therefore, implementing the (incorrect) probit probability distribution would not significantly change the risk estimates.

Results and Conclusions

4.5. "The C/BR exposure characterization is based on a series of unsupported assumptions that contribute to a highly uncertain risk estimate." (EFED, p. 15) All risk assessments are based on assumptions, and we agree that uncertainty about the assumptions

[1] Warren-Hicks W, Parkhurst BJ, Butcher JB. 2002. Methodology for aquatic ecological risk assessment. pp. 345-382 in *Species Sensitivity Distributions in Ecotoxicology.* Leo Posthuma, Glenn Suter, Theo Trass, eds. Lewis Publishers, New York.

contributes to the uncertainty of the risk estimate. In fact, the fundamental objective of probabilistic risk assessment is to incorporate uncertainty about the model assumptions into the risk estimate. The alternative is to ignore uncertainty about the model parameters and thereby be unable to quantify the uncertainty in the risk estimate. The PERA report included considerable discussion about each of the assumptions. Parameters whose values could not be estimated from field and experimental data (and were in that sense "unsupported") were addressed by sensitivity analysis.

4.6. "Field data would appear to support these higher assumptions for exposure. Low-to-no predictions of risk in C/BR's assessment are not substantiated in the field." (EFED, p. 15) Field data indicate that a large percentage of predators contain rodenticide residues in their bodies, which is consistent with the output of the cumulative dose model. The field data indicate that brodifacoum-related mortalities sometimes occur but they do not indicate *risk*, which is the *likelihood* of effect. In particular, field data do not allow estimation of the probability that an individual predator or scavenger will ingest a lethal dose of brodifacoum, which was the objective of the PERA. The fact that field mortalities have been observed (again, consistent with the model, which estimates non-zero mortality for some species under some circumstances) does not imply that risk is high, or cast doubt on a model that estimates low risk. EFED's statement (quoted above) implies that they will reject *any* model showing low risk, no matter how sound the analysis.

Uncertainty

4.7. "A quantitative uncertainty analysis or bounding analysis to improve the risk characterization is not provided.…A major deficiency with the current model which severely limits its utility is its failure to address the important variables mentioned above and to account adequately for uncertainty in the parameters it does address." (EFED, p. 15-16) The PERA includes a quantitative analysis of the sensitivity of model output to the value of many of the model parameters, such as mean PT (Table 9, Table 16, Figure 9, Figure 13, Figure 24), day-to-day variation in PD (Figure 10), halflife (Table 8, Table 15, Figure 12, Figure 23), run duration (Table 10), and the sensitivity of the surrogate species (Figures 17 through 21). The output distribution from each model run incorporates the variability in FIR, PD, C, and individual sensitivity (dose-response). It is not clear what additional uncertainty analysis EFED would suggest to improve the risk characterization.

Appendix A

Brodifacoum concentrations in rat carcasses (pellets, saturation baiting). Page reproduced from Edwards and Swaine (1983).

TABLE 10 Residues of Brodifacoum in 25 Whole Rat Carcasses found Dead above Ground

Farm ref.	Weight of carcass (kg)	Brodifacoum cis isomer (mg/kg)	Brodifacoum trans isomer (mg/kg)	cis: trans	Total brodifacoum residues (mg/kg)	Total brodifacoum per carcass (mg)
A	0.164	0.50	0.22	69:31	0.71	0.12
B	0.254	0.06	0.03	68:32	0.09	0.02
	0.360	2.9	1.3	69:31	4.2	1.5
D	0.104	6.2	4.6	57:43	11	1.1
F*	0.526	0.03	0.02	60:40	0.05	0.02
	0.510	<0.02	<0.02	-	<0.04	<0.02
	0.528	0.03	0.02	60:40	0.05	0.03
	0.435	1.7	1.4	55:45	3.1	1.3
	0.348	0.38	0.20	66:34	0.58	0.20
	0.419	0.11	0.09	55:45	0.19	0.08
G	0.332	<0.02	<0.02	-	<0.04	<0.02
	0.451	<0.02	<0.02	-	<0.04	<0.02
H	0.235	0.22	0.11	67:33	0.32	0.08
	0.360	<0.02	<0.02	-	<0.04	<0.02
	0.406	0.25	0.08	75:25	0.34	0.14
	0.323	0.09	0.05	65:35	0.14	0.04
	0.320	3.1	1.2	73:27	4.3	1.4
	0.466	0.36	0.10	77:23	0.46	0.21
	0.089	0.05	0.04	55:44	0.09	<0.02
I	0.361	0.84	0.71	54:46	1.5	0.56
	0.248	<0.02	<0.02	-	<0.04	<0.02
J	0.446	4.3	1.6	73:27	5.9	2.6
	0.054 (partly eaten)	1.4	0.71	66:34	2.1	0.11
K	0.449	0.46	0.16	74:26	0.61	0.31
	0.231	0.21	0.16	57:43	0.37	0.09

* Other anticoagulant rodenticides used at this site.

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